New benzamides as PPARγ modulators

The present invention relates to new benzamides acting as PPARγ and PPARγ /PPARδ modulators, as well as to processes and intermediates useful for their preparation, and to pharmaceutical compositions containing them.

BACKGROUND ART

Peroxisome proliferator activated receptors (PPARs) belong to the superfamily of transcription factors known as nuclear receptors. This family includes steroid, retinoid and thyroid hormone receptors. Three sub-types of PPARs have been identified in humans, rodents and *Xenopus*. They are PPARα, PPARβ/δ and PPARγ, each encoded by a different gene and showing different tissue distribution.

The gene encoding for PPARγ is transcribed in humans in three different mRNA isoforms (PPARγ1, PPARγ2 and PPARγ3) through different splicing and promoter usage (Fajas et al., *J. Biol. Chem.* **1997**, *272*, 18779-18789). The PPARγ1 isoform shows a wide tissular distribution, while PPARγ2 and PPARγ3 are confined to certain tissues: PPARγ2 is expressed only in adipose tissue and PPARγ3 in adipose tissue as well as in macrophages (Fajas et al., *FEBS Lett.* **1998**, *438*, 55-60).

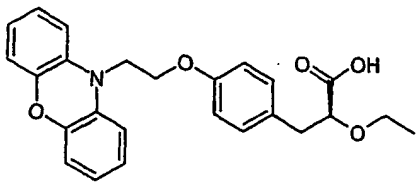
Differences detected in tissue distribution as well as in the activation profile of the PPARγ isoforms suggest they are involved in a variety of physiological functions playing a central role in homeostasis and lipid metabolism (Vamecq et al., *Lancet* **1999**, *354*, 141-148). These functions include, for

example, lipidic transport in plasma and catabolism of fatty acids, regulation of insulin sensitivity and blood glucose levels, differentiation of macrophages that form atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte differentiation, the latter being the most verified function of the PPARγ (Grimaldi, *Prog. Lipid Res.* **2001**, *40*, 269-281, Schiller et al., *J. Biol. Chem.* **2001**, *276*, 14133-14137). Thus, the discovery of these transcription factors has provided new pharmacological targets for the development of useful therapeutic agents for the prevention and treatment of metabolic diseases such as diabetes, obesity and dyslipidaemia.

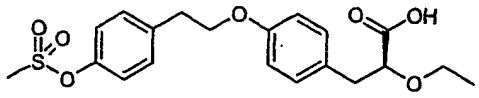
Non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes is characterized by an insulin resistance in peripheral tissues, including muscle, liver, and adipose tissue. Glitazones, selective PPARγ agonist compounds, are drugs that reduce insulin resistance and lower blood glucose levels. Currently two products belonging to this family, rosiglitazone and pioglitazone, have been approved for the treatment of type 2 diabetes in humans.

A great effort has been made in recent years to design new drugs that improve the side effect profile of the first glitazones, show a greater affinity as a PPARγ ligands, and increase their potency in type 2 diabetes. This rational design has yielded structurally diverse compounds that show great potency and selectivity. Among them is interesting to highlight the 2-alkoxyphenylpropionic type derivatives ragaglitazar (1, EP 1049684) and tesaglitazar (2, EP

1084103). These compounds are currently in phase III and II of clinical development, respectively.



(1)



(2)

The use of compounds totally or partially blocking PPARγ activity is useful for the inhibition of adipocyte differentiation, which constitutes an effective treatment for obesity.

PPARδ activation has been shown to lead to increased levels of HDL cholesterol in db/db mice (Leibowitz et al, FEBS Lett. **2000**, *473*, 333-336), and in diabetic-obese rhesus monkeys, while lowering the levels of LDL, triglycerides, and insulin (Oliver et al, *Proc Nat Acad Sci USA*, **2001**, *98*, 5306-5311). The involvement of PPARδ in fatty acid oxidation in muscles was further substained in PPARα knock-out mice (Muoio *et al.*, *J. Biol. Chem.* **2002**, *277*, 26089-26097). A number of PPARδ compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (e.g. WO 02/59098, WO 01/603, WO 01/25181, WO 02/14291, WO 01/79197, WO 99/4815, WO 97/28149, WO 98/27974, WO 97/28115, WO 97/27857, WO 97/28137, WO 97/27847). Taken together, these observations suggest that PPARδ activation is useful in the treatment and prevention of cardiovascular diseases and conditions including atherosclerosis, hypertriglyceremia and mixed dyslipidemia

(WO 01/00603) *In vitro* studies investigating the pharmacological modulation of PPARδ suggest that this kind of ligands may prove to be efficacious drugs for decreasing cardiovascular disease associated with metabolic syndrome, a condition comprised of a cluster of risk factors that also includes insulin resistance, obesity and hypertension (Mukjerheer, *Drug News Perspect.* **2002**, *15*, 261-267).

Pro-differentiation and lipid accumulation effects have been reported in rodent and cultured human keratinocytes, as well as protection against cell death upon PPARδ activation (Tan *et al.*, *Genes Dev.* **2001**, *15*, 3263-3277; Schmuth *et al.*, *J. Invest. Dermatol.* **2004**, *122*, 971-983). Modulators of these activities could be useful for treating a variety of skin disorders.

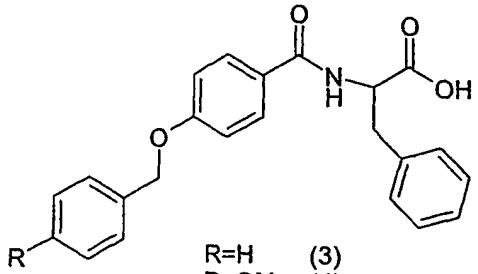
In addition, PPARδ has been implicated as a direct target in colorectal carcinogenesis in mice. All the evidences suggest that PPARδ expression may promote tumour growth and, thus, may be also a potential target for the treatment of colorectal cancer (e.g. Park *et al.*, *Proc Nat Acad Sci USA*, **2001**, *98*, 2598-2603). While PPARγ is acknowledged as a master regulator of adipogenesis, PPARδ may also play a role in adipocyte differentiation, as demonstrated by *in vitro* and in PPARδ-deficient animals, promoting PPARγ gene expression, which upon specific ligand activation promotes adipogenesis. Thus a non-selective PPARγ/δ antagonist would be also a potential drug for obesity (Shearer *et al.*, *Curr. Med. Chem.* **2003**, *10*, 267-280).

This indicate that research for compounds displaying various degrees of PPARγ and PPARδ modulation should lead to the

discovery of drugs that have great potential in the treatment of diseases such as type-2 diabetes, dyslipidemia, syndrome X, cardiovascular diseases (including atherosclerosis), hypercholesteremia, colon cancer, skin disorders (including psoriasis, and wound healing, Tan *et al.*, *Expert Opin. Ther. Targets*, **2004**, *8*, 39), and bone diseases (Pei *et al.*, *J. Clin. Invest.*, **2004**, *113*, 805-806).

Consequently, it is of great interest to provide new therapeutic agents that selectively modulate PPARγ, and PPARγ / PPARδ.

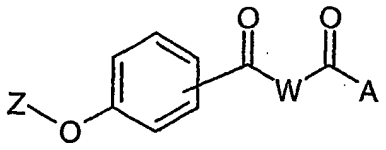
Kundu and collaborators have described benzamides (3), (4) and (5) as *N*-□-glucosidase inhibitors (*Comb. Chem. High.* **2002**, *5*, 545-550). These compounds are structurally close to those of this invention, but were described for different uses.



R=H (3)
R=OMe (4)
R=Br (5)

SUMMARY OF THE INVENTION

One aspect of the present invention relates to the provision of new compounds of formula (I),



(I)

its stereoisomers and mixtures thereof, its polymorphs and mixtures thereof, and the pharmaceutically acceptable solvates and addition salts of all of them, wherein the central benzene ring may be substituted in *meta*- or *para*-position and,

-A is a radical selected from the group consisting of -OR1, -NR2OR1 and -NR2R3; wherein R1, R2 and R3 independently represent -H or -(C_1-C_4)-alkyl;

-W- is a biradical selected from the group: -NH-CH(E)-, -N(E)-CH_2-, and -N(D)-CH_2-CH_2-; wherein E is a radical of the -G-I-J-K type and D is a radical of the -G-I'-J-K type where:

-G - is a bond or a -$(CH_2)_{1-4}$- biradical;

-I - is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -

CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

b) a five- or six-membered aromatic heterocycle containing from one to three heteroatoms selected from O, S and N, this heterocycle being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

c) benzene or benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, this bicyclic system

being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-J- is a bond or a biradical selected from the following groups:

a) -$(CH_2)_{1-4}$-alkylidene;

b) -O-, -S-, -SO-, $-SO_2$-, -CO-, -OCO-, -COO-, -OCONR2-, -NR2COO-, -CONR2-, -NR2CO-, -NR2-, -$NR2SO_2$-, -SO_2NR2-; and

c) -O-(C_1-C_4)-, -(C_1-C_4)-O-, -S-(C_1-C_4)-, -(C_1-C_4)-S-, -SO-(C_1-C_4)-, -(C_1-C_4)-SO-, -SO_2-(C_1-C_4)-, -(C_1-C_4)-SO_2-, -OCO-(C_1-C_4)-, -COO-(C_1-C_4)-, -(C_1-C_4)-OCO-, -(C_1-C_4)-COO-, -OCONR2-(C_1-C_4)-, -NR2COO-(C_1-C_4)-, -(C_1-C_4)-OCONR2-, -(C_1-C_4)-NR2COO-, -CONR2-(C_1-C_4)-, -NR2CO-(C_1-C_4)-, -(C_1-C_4)-CONR2-, -(C_1-C_4)-NR2CO-, -NR2-(C_1-C_4)-, -(C_1-C_4)-NR2-, -SO_2NR2-(C_1-C_4)-, -$NR2SO_2$-(C_1-C_4)-, -(C_1-C_4)-SO_2NR2-, -(C_1-C_4)-$NR2SO_2$-;

-K is a radical selected from the following groups:

a) -H;

b) (C_1-C_4)-alkyl;

c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all

of them optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

d) a radical from a five- or six-membered heterocycle containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

e) phenyl or phenyl optionally substituted by one or several radicals independently selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally

substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-I'- is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

b) a five- or six-membered aromatic heterocycle containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

c) benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-Z is a radical selected from the following groups:

a) -Q-I-J-T wherein

-Q- is a biradical $-(CH_2)_{1-3}-$;

-I- is as defined above;

-J- is as defined above; and

-T is a radical selected from the following groups:

a.a) -H;

a.b) (C_1-C_4)-alkyl;

a.c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all of them optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

a.d) a radical from a five- or six-membered heterocycle containing from one to three heteroatoms selected from O, S and N, this heterocycle being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally

substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

a.e) phenyl or phenyl optionally substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

a.f) a radical from a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F,

and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

b) $-(CH_2)_s-X-P-I-J-T$ wherein

s is 2 or 3;

-X- is selected from the group consisting of -O-, -S-, -SO-, $-SO_2-$ and -NR4-, being R4 a radical selected from the group:

b.a) -H;

b.b) (C_1-C_{10})-alkyl;

b.c) cycloalkyl, cycloalkyl-CO-, cycloalkyl-(C_1-C_3)-alkyl and cycloalkyl-(C_1-C_3)-alkanoyl, wherein the cycloalkyl is a five- or six-membered ring optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and -(C_1-C_4)-alkoxyl optionally substituted by one or several OH or F;

b.d) phenyl, phenyl-CO-, phenyl-(C_1-C_3)-alkyl and phenyl-(C_1-C_3)-alkanoyl, being this aromatic ring optionally substituted by one or several radicals selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl,

(C_1-C_4)-alkanoyloxy,
(C_1-C_4)-alkylsulphinyl,
(C_1-C_4)-alkylsulphenyl,
(C_1-C_4)-alkylsulphonyl,
(C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

b.e) a heterocycle, heterocycle-CO, heterocycle-(C_1-C_3)-alkyl and heterocycle-(C_1-C_3)-alkanoyl, wherein the heterocycle is a five- or six-membered ring containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is a bond or a -$(CH_2)_{1-4}$- biradical;

-I- is as defined above;

-J- is as defined above; and

-T is a radical as defined above;

c) -$(CH_2)_u$-CO-NR5-P-I-J-T wherein

u is 1 or 2;

-R5 is a radical selected from the group:

c.a) -H;

c.b) (C_1-C_{10})-alkyl;

c.c) cycloalkyl and cycloalkyl-(C_1-C_3)-alkyl, wherein the cycloalkyl is a five- or six-membered ring optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

c.d) phenyl and phenyl-(C_1-C_3)-alkyl, being this aromatic ring optionally substituted by one or several radicals selected from -OH, -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl

optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

c.e) a heterocycle and heterocycle-(C_1-C_3)-alkyl, wherein the heterocycle is a five- or six-membered ring containing from one to three heteroatoms selected from O, S and N, being this heterocyclo optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or severalseveral -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is as defined above;

-I- is as defined above;

-J- is as defined above; and

-T is as defined above;

d) -$(CH_2)_s$-NR6R7, wherein s is as defined above, and R6 and R7 together with the N are joined forming a five- or six-membered cycle optionally containing from one to three additional heteroatoms selected from O, S and

N, and that may be fused or substituted by one or two five- or six-membered cycles optionally containing one or several heteroatoms selected from the group composed of O, S and N, all the cycles being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

e) $-(CH_2)_u$-CO-NR6R7 wherein u is as defined above, and R6 and R7 are as defined above;

with the proviso that compound of formula (I) is neither 2-(4-benzyloxybenzoylamino)-3-phenylpropionic acid, nor 2-[4-(4-methoxybenzyloxy)benzoylamino]-3-phenylpropionic acid, nor 2-[4-(4-bromobenzyloxy)benzoylamino]-3-phenylpropionic acid.

In a particular embodiment of this aspect of the invention, in the compounds of formula (I), -W- is -NH-CH(E)-. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the -Q-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the $-(CH_2)_s$-X-P-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the $-(CH_2)_s$-O-P-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the $-(CH_2)_2$-NR4-P-I-J-T type. In another

particular embodiment -W- is -N(E)-CH_2-CH_2-. In another particular embodiment -W- is -N(E)-CH_2-CH_2-, and -Z is a radical of the -Q-I-J-T type. In another particular embodiment -W- is -N(E)-CH_2-CH_2-, and -Z is a radical of the -$(CH_2)_s$-X-P-I-J-T type. In another particular embodiment -W- is -N(E)-CH_2-CH_2-, and -Z is a radical of the -$(CH_2)_s$-O-P-I-J-T type. In another particular embodiment -W- is -N(E)-CH_2-CH_2-, and -Z is a radical of the -$(CH_2)_2$-NR4-P-I-J-T type. In another particular embodiment -A is a radical of the -OR1 type.

Preferred compounds of the present invention include:

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(4-butoxybenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(3-bromobenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-chlorobenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-fluorobenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(3-methylbenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(3-trifluoromethylbenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-methoxybenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-methylbenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-trifluoromethylbenzyloxy)benzoylamino]propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-*o*-tolylethoxy)benzoylamino]propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[3-(4-propoxyphenoxy)propoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(3-methoxybenzyloxy)benzoylamino]propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-ethoxybenzyloxy)benzoylamino]propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(4-butylbenzyloxy)benzoylamino]propionic acid methyl ester;
(2*S*)-2-[4-(4-butylbenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester;
(2*S*)-2-{4-[2-(3-methylquinoxalin-2yloxy)ethoxy]benzoylamino}-3-phenylpropionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-[4-(2-pyridin-2-ylethoxy)benzoylamino]propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(pyridin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(quinolin-8-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(quinolin-7-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(quinolin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[3-(3-methylquinoxalin-2-yloxy)propoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-bromophenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;
(2*S*)-3-(4-fluorophenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester;

(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid ethyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid isopropyl ester;
(2*S*)-3-(4-benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid propyl ester;
(2*S*)-2-(4-benzyloxybenzoylamino)-3-(4-benzyloxyphenyl)propionic acid;
(2*S*)-2-[4-(3-benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid;
3-{(3-benzyloxybenzyl)-[4-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid;
3-((3-benzyloxybenzyl)-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino)propionic acid;
3-{(3-benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid;
2-[4-(4-benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid;
(2*S*)-2-[3-(4-benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid;
3-(4-benzyloxyphenyl)-2-[3-(biphenyl-4-ylmethoxy)benzoylamino]propionic acid;
2-[4-(3-benzyloxybenzyloxy)benzoylamino]-3-(4-bromophenyl)propionic acid;
3-(4-benzyloxyphenyl)-2-[4-(4-butylbenzyloxy)benzoylamino]propionic acid;
2-[4-(4-butylbenzyloxy)benzoylamino]-3-cyclohexylpropionic acid;
{(3-benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}acetic acid;
3-{(3-benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}propionic acid;

3-(4-benzyloxyphenyl)-2-[4-(2-bromobenzyloxy)benzoylamino]propionic acid;
3-(4-benzyloxyphenyl)-2-[4-(2-chlorobenzyloxy)benzoylamino]propionic acid;
3-(4-benzyloxyphenyl)-2-[4-(2-methylbenzyloxy)benzoylamino]propionic acid;
3-(4-benzyloxyphenyl)-2-[4-(3-trifluoromethylbenzyloxy)benzoylamino]propionic acid; and
3-(4-benzyloxyphenyl)-2-[4-(2-trifluoromethylbenzyloxy)benzoylamino]propionic acid.

Throughout the description and claims, the terms (C_1-C_4)-alkyl, (C_1-C_{10})-alkyl, (C_1-C_4)-alkoxyl, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl and (C_1-C_4)-alkanoyloxy shall be construed as straight or branched.

Some of the compounds of formula (I) of the present invention may have one or several chiral centres. The present invention includes each one of the possible stereoisomers and mixtures thereof, particularly racemic mixtures thereof. A single enantiomer may be prepared by any of the commonly used processes, for example, by chromatographic separation of the racemic mixture on a stationary chiral phase, by resolution of the racemic mixture by fractional crystallisation techniques of the diastereomeric salts thereof, by chiral synthesis, by enzymatic resolution or by biotransformation.

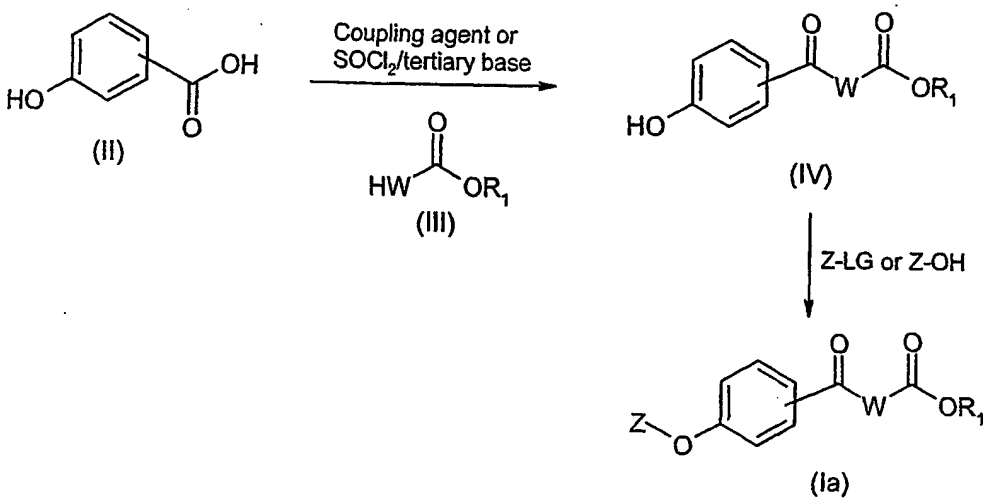
Pharmaceutically acceptable salts include, among others, addition salts of inorganic acids such as hydrochloric, hydrobromic, nitric, sulphuric and phosphoric, as well as addition salts of organic acids such as acetic, benzenesulphonic, benzoic, camphorsulphonic, mandelic,

methanesulphonic, oxalic, succinic, fumaric, tartaric, and maleic. Likewise, an acid proton in compounds of formula (I) may be substituted by a metallic ion, for example, an alkaline metal ion, an alkaline-earth metal ion or an aluminium ion; or may be coordinated with an organic or inorganic base. An acceptable organic base includes diethylamine and triethylamine. An acceptable inorganic base includes aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, and sodium hydroxide. There may be more than one cation or anion depending on the number of functions with charge and on the valency of cations and anions.

Some of the compounds of formula (I) of the present invention may exist in unsolvated as well as solvated forms such as, for example, hydrates. The present invention encompasses all such above-mentioned forms which are pharmaceutically active. Some of the compounds of general formula (I) may exhibit polymorphism, encompassing the present invention all the possible polymorphic forms, and mixtures thereof.

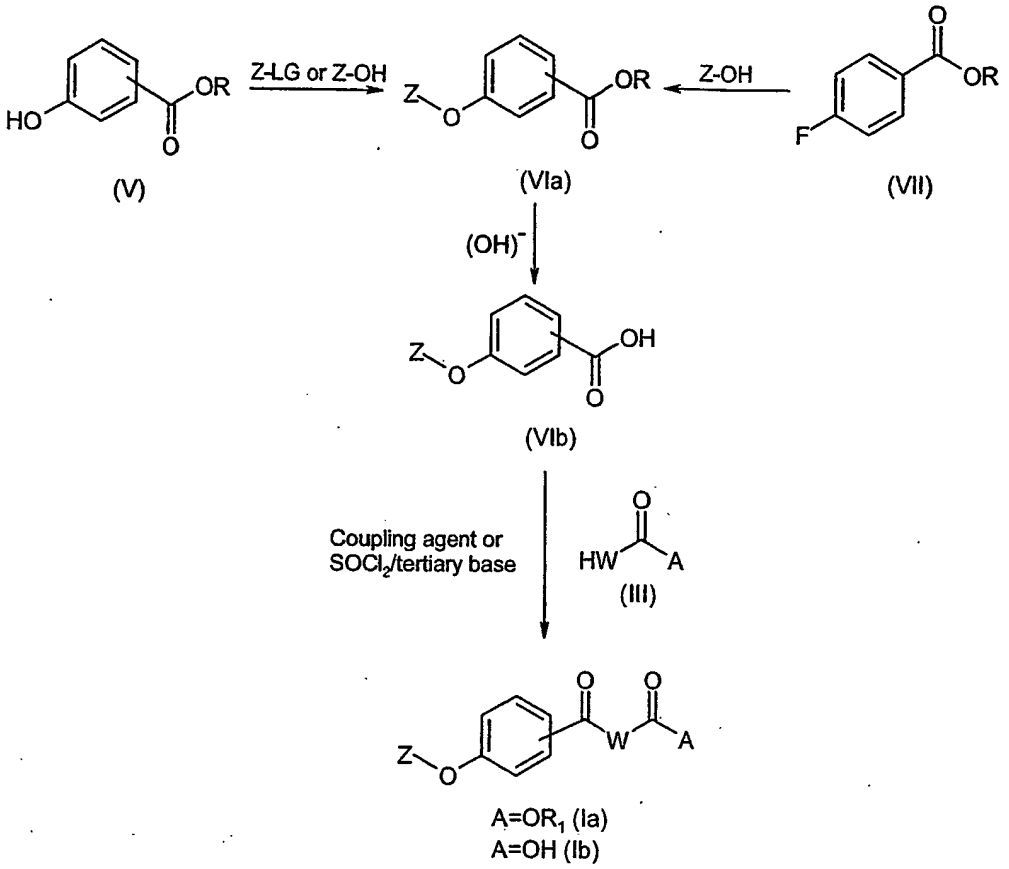
Compounds of general structure (I) may be prepared following various processes perfectly known by any skill person in the field of organic synthesis. Compounds of the present invention may be synthesized using the methods described below, as well as other processes known in the field of organic synthesis. Preferred methods include, but are not limited to, the general processes shown in the attached schemes.

Method A



According to a first method (Method A), the phenolic acid (II) is treated with the amine derivative (III) in the presence of a suitable coupling agent, for example the combination of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT), or with thionyl chloride in the presence of a tertiary base such as triethylamine (Elmore, *Amino Acids Pep. Proteins* **2001**, *32*, 107-162). Final compounds (Ia) are obtained by Williamson etherification by displacement of a leaving group (LG) bonded to a type -Z radical with the phenol (IV) (using for example NaH, K_2CO_3 or Cs_2CO_3 as a base in a solvent such as DMF or acetone; (Bal-Tembe et al., *Bioorg. Med. Chem.* **1997**, *5*, 1381-1388; Cantello et al., *J. Med. Chem.* **1994**, *37*, 3977-3985, Solar et al., *J .Org. Chem.* **1966**, *31*, 1996-1997; EP 875510), or by Mitsunobu reaction between (IV) and a Z-OH type alcohol in the presence of, for example, diethyl azodicarboxylate (DEAD) and triphenylphosphine in tetrahydrofurane as a solvent (Mitsunobu, *Synthesis* **1981**, 1; Hughes, *Org. React.* **1992**, *42*, 335).

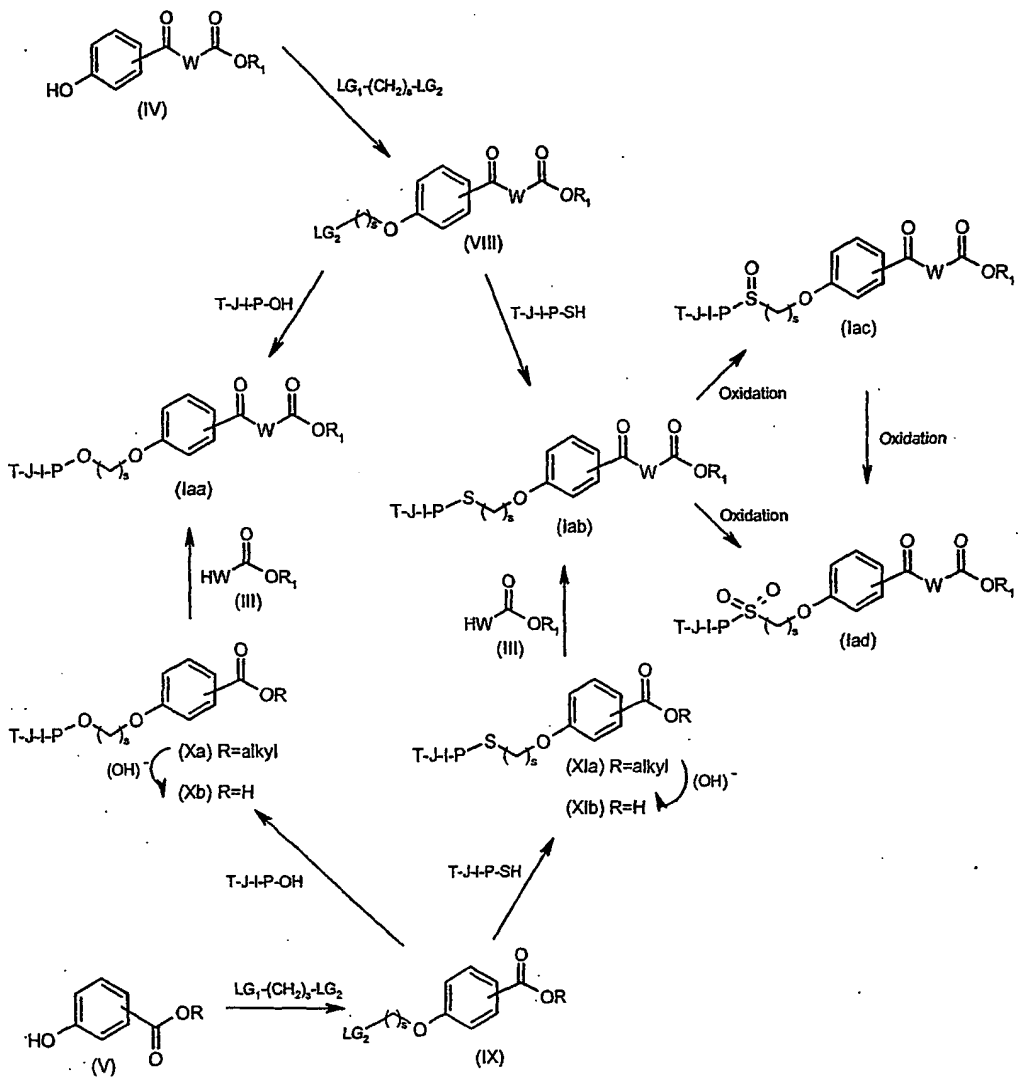
Method B



An alternative strategy (Method B) involves prior alkylation of the phenolic esters (V). After basic hydrolysis of the resulting ester, the final compounds (I) are synthesized by reaction with the amine derivative (III). Alternatively, and only in the specific case of *para* substitution of the aromatic ring, the phenolic ether (VI) may be formed by aromatic nucleophilic substitution starting from the fluorinated compound (VII).

When -Z is a radical of the $-(CH_2)_s$-X-P-I-J-T type where X is O or S, for the alkylation of the phenol another alternative procedure may be followed (Method C).

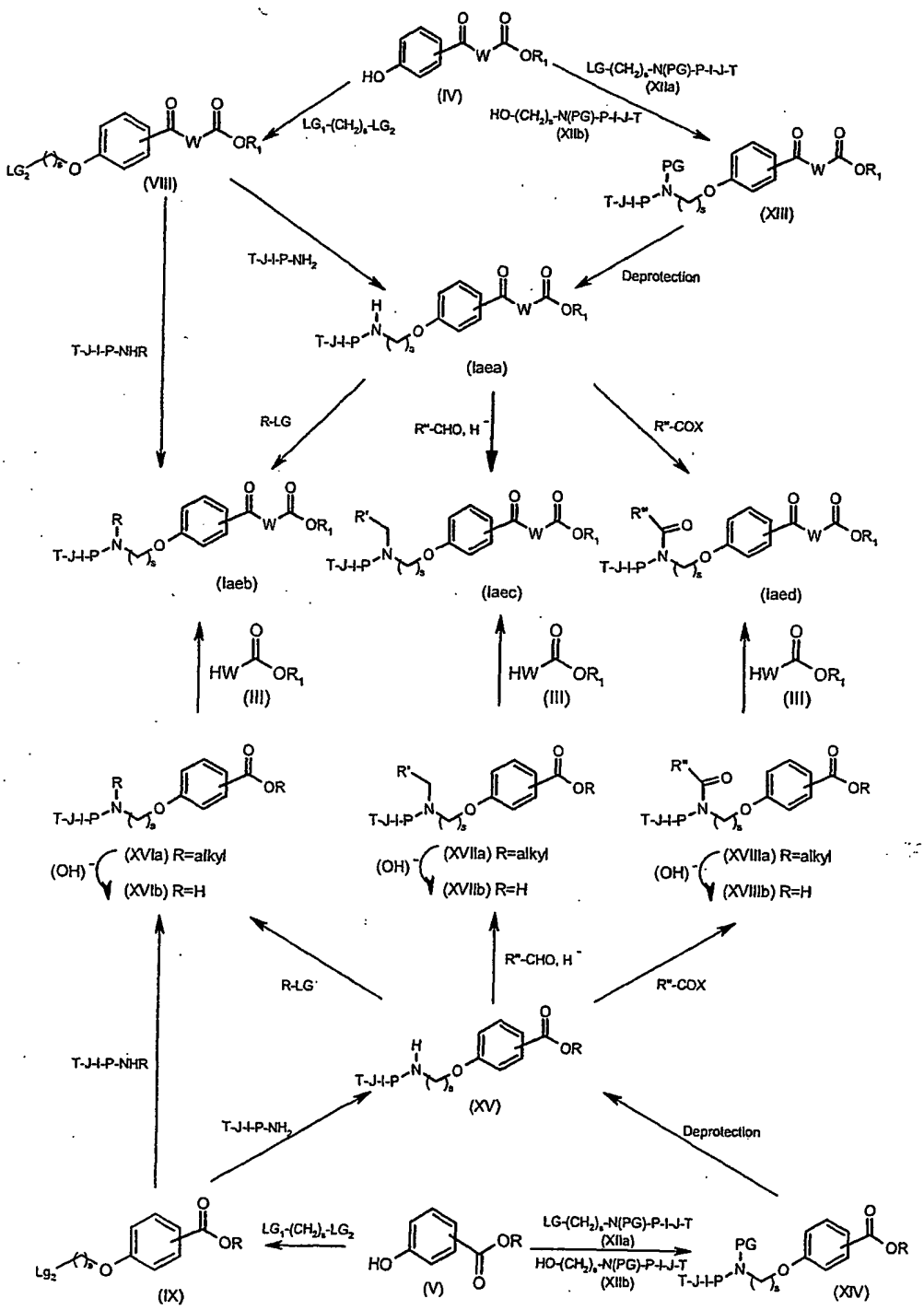
Method C



The phenol (IV) or (V) is treated with the suitable doubly functionalised alkylidene derivative (EP 875510) and, then, a nucleophilic substitution reaction with the desired alcohol or thiol is carried out to obtain the compounds (Iaa), and (Iab) or the esters (Xa) and (XIa), depending on the initial phenol. The hydrolysis of the esters (Xa) and (XIa) and their subsequent reaction with the amine derivative (III) also leads to the compounds (Iaa) and (Iab). The derivatives of

the sulphoxide (Iac) and sulphone (Iad) types are obtained by oxidation of the corresponding thioether (Iab) in the presence of oxidizing agents such as, for example, hydrogen peroxide or *m*-chloroperbenzoic acid.

Method D

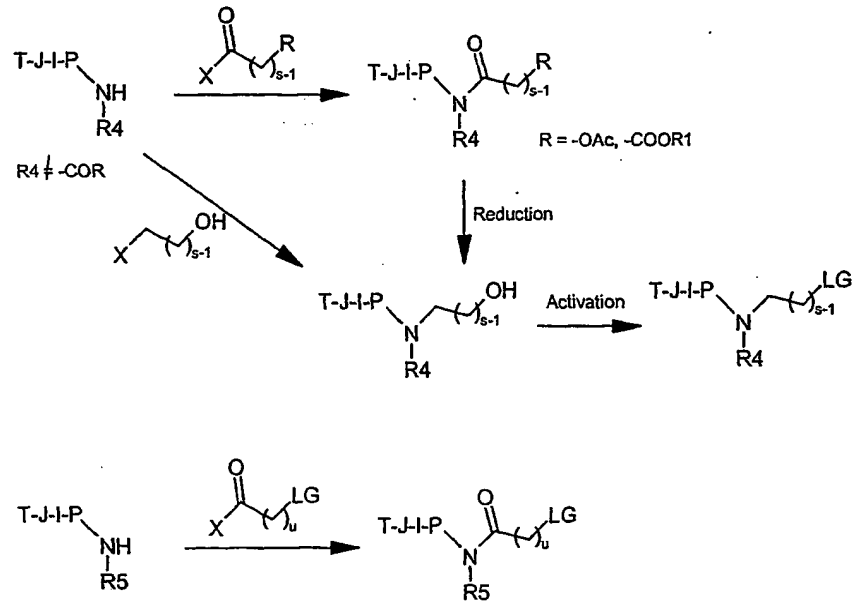

(IV)
LG-(CH2)s-N(PG)-P-I-J-T
(XIIa)
HO-(CH2)s-N(PG)-P-I-J-T
(XIIb)
LG1-(CH2)s-LG2
(VIII)
(XIII)
T-J-I-P-NH2
Deprotection
T-J-I-P-NHR
(Iaea)
R-LG
R"-CHO, H
R"-COX
(Iaeb)
(Iaec)
(Iaed)
(III)
(XVIa) R=alkyl
(XVIb) R=H
(XVIIa) R=alkyl
(XVIIb) R=H
(XVIIIa) R=alkyl
(XVIIIb) R=H
(XV)
(IX)
(V)
(XIV)

When -Z is a radical of the $-(CH_2)_s$-NR4-P-I-J-T type, the amines (Iae) may be obtained starting from the phenols (IV) or (V) following two alternative alkylation routes in every case (Method D). In the case of phenol (IV), the reaction with a doubly functionalised alkylidene derivative and, then, the nucleophilic substitution with the desired amines; or the etherification with the protected amine compound (XII) (as a trifluoroacetamide derivative, for example), and subsequent functionalisation of the amine released after its deprotection (in a basic medium, or with $NaBH_4$ (Harland and Hodge *Synthesis* **1984**, 941-943)) yields the desired compounds. The tertiary amines of the (Iaeb) and (Iaec) types are obtained by the treatement of the compound (Iaea) with alkylating agents or by reductive alkylation, respectively. The amides (Iaed) are synthesized by acylation of the compound (Iaea) with the corresponding acid derivative in the presence of a tertiary amine, or by treating the secondary amine with an acid in the presence of a coupling agent such as, for example the combination of EDC and HOBT (Elmore, *Amino Acids Pep. Proteins* **2001**, *32*, 107-162). In the case of the phenol (V), the amines (Iae) are obtained by reaction of their precursor acids (XVIb), (XVIIb) and (XVIIIb) with the amine derivatives (III) following the methods outlined above. These acids, in turn, are obtained from the phenol (V) following an analogous process to that used in the case of the phenol (IV).

The Z-OH or Z-LG type compounds are products that have already been described. Some of them are commercially available or may be prepared following methods analogous to those used to synthesize others that are already known, such as those that are explained in detail in the following documents: EP 03062228; WO 97/31907; WO 01/00603; Daoud et

al., *J. Indian Chem. Soc.* **1989**, *66*, 316-318 and Aquino, *J. Med. Chem.* **1996**, *39*, 562-569, some of them summarised in Scheme 1.

Scheme 1

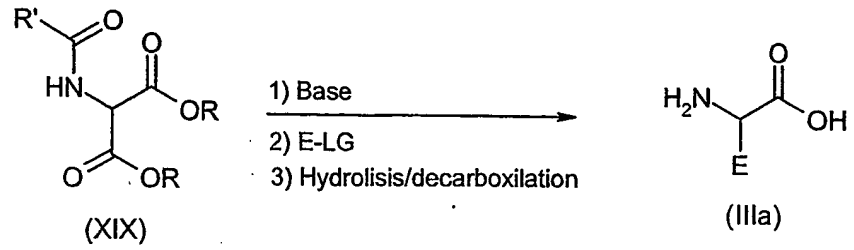


Some of the compounds (III) are commercially available products, particularly when they are α-amino acids. Others have already been described or may be synthesized following various routes, most of which have been described (March, *Advanced Organic Chemistry*, **1991**, Ed. John Wiley & Sons; Juaristi, *Enantioselective Synthesis of β-Amino Acids*, **1997**, Ed. Wiley-VDH).

An approach for the preparation of the α-amino acids (W is -NH-CH(E)-) is the Sorensen synthesis (Mori, *Tetrahedron* **1985**, 2369-2377; Scheme 2), wherein dialkyl

acyl-amide-malonate is alkylated in a basic medium and, after subsequent hydrolysis and decarboxylation, the desired α-amino acids (IIIa) are obtained.

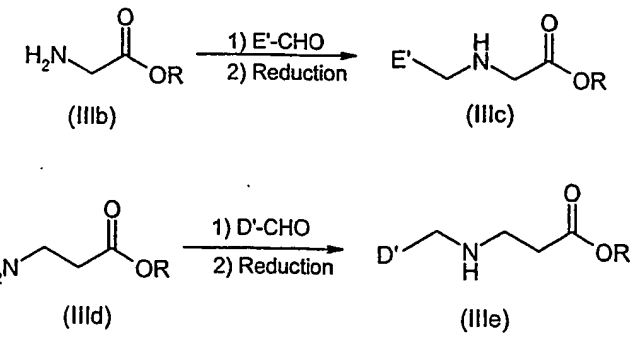
Scheme 2

The 

(XIX) (IIIa)

N-Substituted glycines and β-alanines (W is $-N(E)-CH_2-$ or $-N(D)-CH_2-CH_2-$) may be synthesized by the methods shown bellow, either by reductive amination of the corresponding glycine or alanine with the suitable aldehyde (Scheme 3) using reducing agents such as $NaBH_4$, $NaBH_3CN$ or $NaBH(AcO)_3$, or by nucleophilic substitution of the esters (XX) or (XXI) with the suitable amine (Scheme 4).

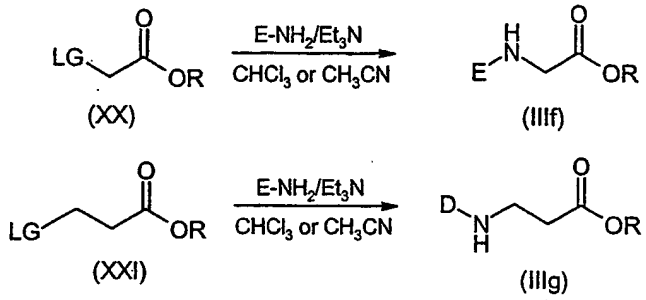
Scheme 3



(IIIb) (IIIc)

(IIId) (IIIe)

Scheme 4

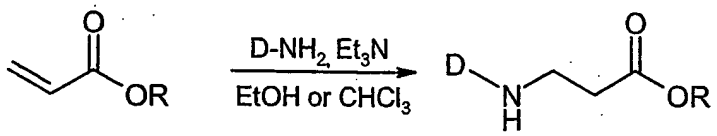


(XX) (IIIf)

(XXI) (IIIg)

An alternative process for the synthesis of β-alanines (III) would be the addition of the corresponding amine to the α,β-unsaturated ester of interest (Scheme 5)

Scheme 5

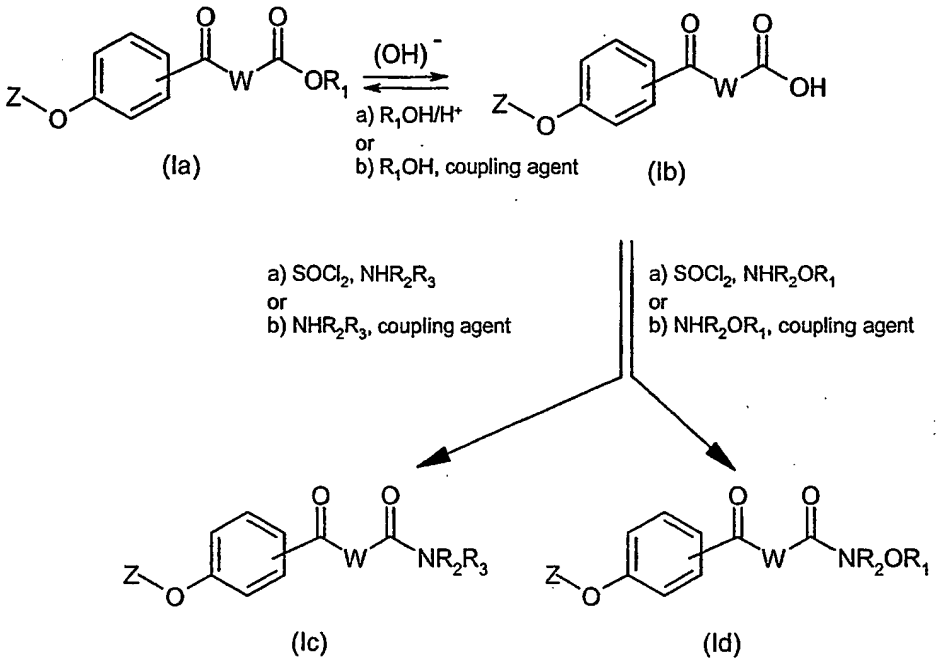


(XXII) (IIIg)

Conversion of a compound of formula (I) into a different one involves transforming the -CO-A group into a different group. The modifications considered are: the hydrolysis of the -COOR1 substituent, wherein -R1 represents a -(C_1-C_4)-alkyl moiety, to yield the corresponding carboxylic acid; the esterification of the carboxylic acids (Ib) with the R1OH alcohols; and, lastly, the amination of the -COOR1 group to obtain the corresponding amides. The hydrolysis methods used are the usual ones, for example, using an alkaline hydroxide

in aqueous methanol. The amination and esterification processes are those commonly used (Scheme 6).

Scheme 6



The compounds of the present invention are ligands of the PPARγ and PPARδ. Therefore, they are expectedly useful for the prophylactic and/or curative treatment of a condition mediated by PPARγ or PPARγ / PPARδ in an animal including a human. Thus, an aspect of the present invention relates to the use of these compounds for the preparation of a medicament for the prophylactic and/or curative treatment of a condition associated with metabolic diseases, particularly non-insulin-dependent diabetes mellitus, obesity, hypercholesterolaemia, and other lipid-mediated pathologies, cardiovascular diseases associated with metabolic syndrome, inflammation and inflammatory processes in general, such as rheumatoid arthritis, atherosclerosis, psoriasis, and intestinal inflammatory disease, bone diseases, particularly osteoporosis, cancer, skin wound healing, and cutaneous

disorders associated with an anomalous differentiation of epidermic cells, particularly the formation of keloids. Therefore, this aspect of the invention is related to a method for the prophylactic and/or curative treatment of an animal, including a human, suffering from the above-mentioned pathologies, which comprises administering a therapeutically effective amount of a formula (I) compound.

Another aspect of the invention relates to pharmaceutical compositions comprising a therapeutically effective amount of the compound (I), as the active ingredient, together with appropiate amounts of pharmaceutically acceptable excipients. Preferably, the compound is administered orally, parenterally or topically.

Throughout the description and claims the word "comprise" and variations of the word, such as "comprising", is not intended to exclude other additives, components, elements or steps. The disclosures in the abstract accompanying this application and in the application from which priority is claimed, are incorporated herein as reference.

Additional objects, advantages and novel features of the invention will be set forth in part in the description, and in part will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as limiting.

EXAMPLES

^{1}H-NMR spectra of the compounds have been recorded using a VARIAN GEMINI-200 MHz and a VARIAN UNITY-300 MHz equipment and chemical shifts are expressed as ppm (δ) from the internal reference TMS. Mass spectra have been obtained with an Agilent 1100 VL mass spectrometer. The nomenclature of the different compounds used in the present document is based on the software AUTONOM (Automatic Nomenclature) from the Beilstein Institute, which uses the IUPAC systematic nomenclature.

INTERMEDIATES (IV)

METHOD A:

To a solution of 1 eq of the aminic derivative (III), 1 eq of the acid (II), 1.3 eq of HOBT, and 1.3 eq of EDC in tetrahydrofurane, the solution being 0.2 M in the aminic derivative, 2 eq of triethylamine were added. The reaction mixture was stirred at room temperature for 18h, and then water and dichloromethane were added. The organic layer was separated, and the aqueous layer was extracted once with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off under reduced pressure and the obtained residue was purified by column chromatography.

METHOD B:

To a solution 0.1 M of 1 eq of the aminic derivative (III) in anhydrous dichloromethane, 2 eq of triethylamine, and 1.2 eq of the corresponding acid chloride, were added. The reaction mixture was either refluxed with stirring (secondary amines) or stirred at room temperature (primary amines) for 18h, then

treated with water, twice with sodium bicarbonate and, finally, with a brine. The solvent was distilled off under reduced pressure and the obtained residue was purified by column chromatography.

METHOD C:

To a solution of 1 eq of the aminic derivative (III), and 1 eq of the corresponding acid chloride in ethyl acetate, the solution being 0.05 M in the aminic derivative, Amberlyst 21 (200 mg/mmol acid chloride) was added. The reaction mixture was either refluxed with stirring (secondary amines) or stirred at room temperature (primary amines). Then, the resin was filtered, and the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography.

TABLE 1

INTERM	
IV.1	(2*S*)-3-(4-Benzyloxyphenyl)-2-(4-hydroxybenzoylamino)propionic acid methyl ester; ^{1}H-NMR: 7.52 (d, 2H), 7.31-7.20 (m, 5H), 6.97 (d, 2H), 6.81 (d, 2H), 6.74 (d, 2H), 4.94 (s,2H), 4.86 (m, 1H), 3.66 (s, 3H), 3.06 (m, 2H)
IV.2	(2*S*)-3-(4-Benzyloxyphenyl)-2-(3-hydroxybenzoylamino)propionic acid methyl ester; MS: 406
IV.3	(2*S*)-3-Cyclohexyl-2-(4-hydroxybenzoylamino)propionic acid methyl ester; MS: 306

INTERMEDIATES (VIa)

METHOD D:

A suspension of 1 eq of phenol (V), 3 eq of anhydrous potassium carbonate, and 1.3 eq of the Z-LG derivative in ethyl acetate, the suspension being aproximately 0.5 M in the phenol (V), was refluxed for 18h. Then, the suspension was allowed to cool down and the white solid was filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

METHOD E:

A suspension of 1 eq of phenol (V), 3 eq of cesium carbonate, 1.3 eq of the Z-LG derivative, and a catalythic amount of potassium iodide in anhydrous dimethylformamide (DMF), the suspension being 0.1 M in the phenol (V), was heatet at 80°C for 18h. Then, the suspension was allowed to cool down at room temperature, and then water and ethyl acetate were added. The organic layer was washed three times with brine, then dried over anhydrous sodium sulfate and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

METHOD F:

To a solution 0.1 M of 1 eq of phenol (V) in anhydrous DMF, containing a catalythic amount of potassium iodide, 1.1 eq of 60% sodium hydride in paraffin were added. The suspension was stirred at room temperature for 10 minutes and then 1.1 eq of the Z-LG derivative were added. The resulting solution was stirred at 80°C for 18h, and then allowed to cool down to room temperature. After treating with water and ethyl acetate, the organic layer was washed three times with brine, then dried over anhydrous sodium sulfate and filtered. The

solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

METHOD G:

To a solution of 1 eq of phenol (V), 2.2 eq of the Z-OH derivative, and 2.2 eq of triphenylphosphine in tetrahydrofurane, the solution being 0.2 M in the phenol, 2.2 eq of DEAD were added under inert atmosphere. The reaction mixture was stirred at room temperature for 18h. Then, the solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

METHOD H:

To a solution 0.01 M of 1 eq of the Z-OH derivative in anhydrous DMF, 1.1 eq of 60% sodium hydride in paraffine were added slowly with stirring until bubbling was finished. Then, 1.2 eq of 4-fluorobenzoic acid methyl ester were added, and the mixture was heated at 80°C for 20h. The resulting solution was carefully poured over water/ice, and the mixture formed was extracted four times with ethyl acetate. The organic extracts were washed five times with brine, then dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

TABLE 2

INTERM	
VIa.1	4-[2-(Dibenzylamino)ethoxy]benzoic methyl ester; ^{1}H-NMR: 8.00 (d, 2H), 7.45-7.20 (m, 10H), 6.85 (d, 2H), 4.05 (t, 2H), 3.90 (s, 3H), 3.75 (s, 4H), 2.91 (t, 2H)
VIa.2	4-[2-(2-Phenyloxazol-4-yl-5-methyl)ethoxy]benzoic acid methyl ester; ^{1}H-NMR: 7.99-7.85 (m, 4H), 7.44-7.38 (m, 3H), 6.88 (d, 2H), 4.23 (t, 2H), 3.85 (s, 3H), 2.98 (t, 2H), 2.36 (s, 3H)
VIa.3	3-[2-Dibenzylamino)ethoxy]benzoic acid methyl ester; ^{1}H-NMR:7.65-7.00 (m, 14H), 4.09 (t, 2H), 3.92 (s, 3H), 3.74 (s, 4H), 2.93 (t, 2H)
VIa.4	3-(4-Butylbenzyloxy)benzoic acid methyl ester; MS: 299
VIa.5	4-(2-Pyridin-2-ylethoxy)benzoic acid methyl ester; MS: 258
VIa.6	4-(2-Naphthalen-2-ylethoxy)benzoic acid methyl ester; MS: 307
VIa.7	4-(4-Butylbenzyloxy)benzoic acid methyl ester; MS: 299
VIa.8	3-(4-Benzyloxybenzyloxy)benzoic acid methyl ester; MS: 349
VIa.9	4-(3-Benzyloxybenzyloxy)benzoic acid methyl ester; MS: 349
VIa.10	3-(3-Benzyloxybenzyloxy)benzoic acid methyl ester; MS: 349

INTERMEDIATES (VIb)

METHOD J:

To a solution 0.1 M of 1 eq of intermediate (VIa) in a mixture of 3:1 tetrahydrofurane:methanol, between 1.5 and 10 eq of lithium hydroxide 1 M in water were added. The resulting mixture was stirred at room temperature for 18h, then treated with HCl 1 N until pH=5-6, and extracted twice with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

METHOD K:

To a solution 0.05 M of 1 eq of intermediate (VIa) in methanol, 5 eq of potassium hydroxide 1.4 M were added. The resulting solution was stirred at room temperature for 18h, then treated with HCl 1 N until acid pH, and extracted with ethyl acetate twice. The organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

TABLE 3

INTERM	
VIb.1	4-[2-(Dibenzylamino)ethoxy]benzoic acid; ^{1}H-NMR: 7.98 (d, 2H), 7.47-7.27 (m, 10H), 6.91 (d, 2H), 4.14 (t, 2H), 3.78 (s, 4H), 2.95 (t, 2H)

VIb.2	4-[2-(2-Phenyloxazol-4-yl-5-methyl)ethoxy]benzoic acid; ^{1}H-NMR: 7.95-7.83 (m, 4H), 7.50-7.46 (m, 3H), 7.01 (d, 2H), 4.28 (t, 2H), 2.95 (t, 2H), 2.35 (s, 3H)
VIb.3	3-[2-(Dibenzylamino)ethoxy]benzoic acid; ^{1}H-NMR: 7.54-7.00 (m, 14H), 4.40 (t, 2H), 4.31 (s, 4H), 3.39 (t, 2H)
VIb.4	4-(3-Benzyloxybenzyloxy)benzoic acid; MS: 335
VIb.5	3-(3-Benzyloxybenzyloxy)benzoic acid; MS: 335
VIb.6	4-(2-Pyridin-2-ylethoxy)benzoic acid; MS: 244
VIb.7	3-(4-Butylbenzyloxy)benzoic acid; MS: 285
VIb.8	4-(2-Naphthalen-2-ylethoxy)benzoic acid; MS: 293
VIb.9	4-(4-Butylbenzyloxy)benzoic acid; MS: 285
VIb.10	3-(4-Benzyloxybenzyloxy)benzoic acid; ^{1}H-NMR: 7.60 (br s, 2H), 7.43-7.22 (m, 8H), 7.10 (dd, 1H), 6.94 (d, 2H), 5.02 (s, 2H), 4.97 (s, 2H)

INTERMEDIATES (VIII)

METHOD L:

To a suspension of 1 eq of phenol (IV), and 2 eq of cesium carbonate in anhydrous DMF, the suspension being 0.4 M in the phenol, 100 eq of LG_1-$(CH_2)_s$-LG_2 were added. The reaction mixture was heated at 90°C for 18h, and then treated with water and 1,2-dichloroethane. The organic layer was washed three times with brine, then dried over anhydrous sodium sulfate and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

TABLE 4

INTERM	
VIII.1	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(2-chloroethoxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.71 (d, 2H), 7.50-7.33 (m, 5H), 7.06 (d, 2H), 6.93-6.89 (m, 4H), 6.58 (d, 1H), 5.07-5.01 (m, 3H), 4.25 (t, 2H), 3.82 (t, 2H), 3.76 (s, 3H), 3.20 (m, 2H)
VIII.2	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(2-chloroethoxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.50-7.25 (m, 8H), 7.10-7.00 (m, 3H), 6.91 (d, 2H), 6.57 (d, 1H), 5.10-5.00 (m, 3H), 4.27 (t, 2H), 3.83 (t, 2H), 3.78 (s, 3H), 3.24 (dd, 1H), 3.16 (dd, 1H)

INTERMEDIATE (Xa), (XVIa) and (XIa)

The following compounds were synthesized according to any of methods D, E or F, starting from intermediates (IX).

TABLE 5

INTERM	
Xa.1	4-[2-(3-Methylquinoxalin-2-yloxy)ethoxy]benzoic acid methyl ester; ^{1}H-NMR: 8.02 (d, 2H), 7.95 (d, 1H), 7.88 (d, 1H), 7.65-7.48 (m, 2H), 7.00 (d, 2H), 4.87 (t, 2H), 4.48 /t, 2H), 3.89 (s,3H), 2.64 (s, 3H)
Xa.2	3-[2-(3-Methylquinoxalin-2-yloxy)ethoxy]benzoic acid methyl ester; MS: 339

XVIa.1	3-[2-(3-Methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoic acid methyl ester; MS: 339
XVIa.2	4-[2-(3-Methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoic acid methyl ester; MS: 339
XIa.1	3-[2-(Thiophen-2-ylsulfanyl)ethoxy]benzoic acid methyl ester; MS: 295

INTERMEDIATE (Xb), (XVIb) and (XIb)

The following compounds were synthesized according to any of methods J or K, starting from intermediates (Xa), (XVIa) or (XIa).

TABLE 6

INTERM	
Xb.1	4-[2-(3-Methylquinoxalin-2-yloxy)ethoxy]benzoic acid; MS: 325
Xb.2	3-[2-(3-Methylquinoxalin-2-yloxy)ethoxy]benzoic acid; MS: 325
XVIb.1	3-[2-(3-Methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoic acid; MS: 325
XVIb.2	4-[2-(3-Methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoic acid; MS: 325
XIb.1	3-[2-(Thiophen-2-ylsulfanyl)ethoxy]benzoic acid; MS: 281

INTERMEDIATE (XIV)

The following compounds were synthesized according to any of methods D to G, starting from phenol (V) and amines (XIIa) or (XIIb).

TABLE 7

INTERM	
XIV.1	3-{2-[Benzyl-(2,2,2-trifluoroacetyl)amino]ethoxy} benzoic acid methyl ester; MS: 382
XIV.2	4-{2-[Benzyl-(2,2,2-trifluoroacetyl)amino]ethoxy} benzoic acid methyl ester; MS: 382

INTERMEDIATE (XV)

The following compounds were synthesized either according to any of methods D to F, starting either from intermediate (IX), and the corresponding amines, or according to method M, from intermediate (XIV).

METHOD M:

To a solution 0.1 M of 1 eq of intermediate (XIV) (PG = trifluoroacetyl) in a mixture of tetrahydrofurane:methanol (3:1), 5 eq of lithium hydroxide 1 M in water were added. The solution was stirred until complete dissolution, then diluted with a mixture of water/ethyl acetate, and then acidified to pH=5 with HCl 1 N. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was disolved in methanol 0.1 M and treated with 3.2 eq of thionyl chloride. The solution was refluxed for 18h, and then allowed to cool down to room temperature. The solvent was distilled

off under reduced pressure and the residual solid was broken up with hexane.

TABLE 8

INTERM	
XV.1	4-(2-Benzylaminoethoxy)benzoic acid methyl ester; ^{1}H-NMR: 7.96 (d, 2H), 7.34-7.21 (m, 5H), 6.89 (d, 2H), 4.12 (t, 2H), 3.87 (s, 2H), 3.85 (s, 3H), 3.10 (t, 2H); MS: 286
XV.2	3-(2-Benzylaminoethoxy)benzoic acid methyl ester; MS: 286

INTERMEDIATE (XVIIIa)

The following compounds were synthesized according to any of methods A to C, starting from intermediate (XV) and the corresponding acids.

TABLE 9

INTERM	
XVIIIa.1	4-[2-(*N*-Benzyl-*N*-benzoylamino)ethoxy]benzoic acid methyl ester; ^{1}H-NMR: 7.99 (d, 2H), 7.43-6.77 (m, 12H), 4.91-4.70 (m, 2H), 4.35-3.65 (m, 4H), 3.90 (s, 3H)
XVIIIa.2	4-{2-[*N*-Benzyl-*N*-(pyridin-3-ylcarbonyl)amino]ethoxy}benzoic acid methyl ester; ^{1}H-NMR: 8.80-6.85 (m, 13H), 4.91-4.69 (m, 2H), 4.36-3.60 (m, 4H), 3.86 (s, 3H)

INTERMEDIATE (XVIIIb)

The following compounds were synthesized according to methods J or K, starting from intermediate (XVIIIa).

TABLE 10

INTERM	
XVIIIb.1	4-[2-(*N*-Benzyl-*N*-benzoylamino)ethoxy]benzoic; ^{1}H-NMR: 8.06 (d, 2H), 7.41-6.81 (m, 12H), 4.94-4.71 (m, 2H), 4.37-3.67 (m, 4H)
XVIIIb.2	4-{2-[*N*-Benzyl-*N*-(pyridin-3-ylcarbonyl)amino]ethoxy}benzoic acid; ^{1}H-NMR: 8.75-6.85 (m, 13H), 4.91-4.72 (m, 2H), 4.36-3.60 (m, 4H)

EXAMPLE (Ia):

The compounds of formula (Ia) shown in Table 11 were synthesized according to any of methods D to G, starting from intermediate (IV):

TABLE 11

Ex.	
1	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-phenylallyloxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.73 (d, 2H), 7.43-7.25 (m, 10H), 7.07 (d, 2H), 6.98 (d, 2H), 6.92 (d, 2H), 6.76 (d, 1H), 6.57 (d, 1H), 6.42 (dt, 1H), 5.10-5.00 (m, 3H), 4.75 (dd, 2H), 3.77 (s, 3H), 3.28-3.16 (m, 2H)
2	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(4-phenoxybenzyloxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.71 (d, 2H), 7.42-6.88 (m, 20H), 6.48 (d, 1H), 5.07-5.04 (m, 5H), 3.77 (s, 3H), 3.25-3.10 (m, 2H)
3	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(biphenyl-4-ylmethoxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.72 (d, 2H), 7.65-7.26 (m, 14H), 7.07-7.00 (m,4H), 6.90 (d, 2H), 6.48 (d, 1H), 5.16 (s, 2H), 5.10-5.00 (m, 3H), 3.77 (s, 3H), 3.30-3.10 (m, 2H)
4	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-phenoxybenzyloxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.70 (d, 2H), 7.43-6.92 (m, 20H), 6.48 (d, 1H), 5.08-5.04 (m, 5H), 3.77 (s, 3H), 3.30-3.10 (m, 2H)
5	(2*S*)-2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid methyl ester; ^{1}H-NMR: 7.70 (d, 2H), 7.43-6.92 (m, 20H), 6.48 (d, 1H), 5.09 (s, 2H), 5.08 (s, 2H), 5.06-5.02 (m, 3H), 3.77 (s, 3H), 3.27-3.14 (m, 2H)

6	(2*S*)-3-(4-Benzyloxyphenyl)-2-(4-phenethyloxybenzoylamino)propionic acid methyl ester; ^{1}H-NMR: 7.69 (d, 2H), 7.42-7.30 (m, 10H), 7.04 (d, 2H), 6.92-6.88 (m, 4H), 6.45 (d, 1H), 5.06-5.00 (m, 3H), 4.22 (t, 2H), 3.77 (s, 3H), 3.27-3.10 (m, 4H)
7	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-phenylpropoxy)benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 7.70 (d, 2H), 7.43-7.22 (m, 10H), 7.06 (d, 2H), 6.93-6.89 (m, 4H), 6.51 (d, 1H), 5.10-5.02 (m, 3H), 4.00 (t, 2H), 3.77 (s, 3H), 3.25-3.15 (m, 2H), 2.83 (t, 2H), 2.12 (m, 2H)
8	(2*S*)-2-[4-(4-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid methyl ester. ^{1}H-NMR: 7.70 (d, 2H), 7.46-7.35 (m, 13H), 7.06-6.97 (m, 7H), 6.89 (d, 2H), 6.49 (d, 1H), 5.09-5.00 (m, 7H), 3.76 (s, 3H), 3.26-3.11 (m, 2H)
9	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(biphenyl-2-ylmethoxy)benzoylamino]propionic acid methyl ester; MS: 572
10	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(3-phenylallyloxy)benzoylamino]propionic acid methyl ester; MS: 522
11	(2*S*)-2-[3-(4-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid methyl ester; ^{1}H-NMR: 7.47-7.26 (m, 15H), 7.13-7.00 (m, 5H), 6.93 (d, 2H), 6.61 (d, 1H), 5.09-5.00 (m, 7H), 3.78 (s, 3H), 3.29-3.15 (m, 2H)
12	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(biphenyl-4-ylmethoxy)benzoylamino]propionic acid methyl ester; MS: 572

13	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(3-phenoxybenzyloxy)benzoylamino]propionic acid methyl ester; MS: 588
14	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(3-phenylpropoxy)benzoylamino]propionic acid methyl ester; MS: 524
15	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(4-butoxybenzyloxy)benzoylamino]propionic acid methyl ester; MS: 568
16	(2*S*)-2-[4-(4-Butoxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; MS: 468
17	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(thiophen-3-ylmethoxy)benzoylamino]propionic acid methyl ester; MS: 488
18	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-bromobenzyloxy)benzoylamino]propionic acid methyl ester; MS: 575
19	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-bromobenzyloxy)benzoylamino]propionic acid methyl ester; MS: 575
20	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-chlorobenzyloxy)benzoylamino]propionic acid methyl ester; MS: 530
21	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-chlorobenzyloxy)benzoylamino]propionic acid methyl ester; MS: 530
22	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-fluorobenzyloxy)benzoylamino]propionic acid methyl ester; MS: 514
23	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-methylbenzyloxy)benzoylamino]propionic acid methyl ester; MS: 496

24	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-trifluoromethylbenzyloxy)-benzoylamino]propionic acid methyl ester; MS: 564
25	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-methoxybenzyloxy)benzoylamino]propionic acid methyl ester; MS: 526
26	(2*S*)-2-[4-(3-Bromobenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; MS: 475
27	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-methylbenzyloxy)benzoylamino]propionic acid methyl ester; MS: 510
28	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-trifluoromethylbenzyloxy)-benzoylamino]propionic acid methyl ester; MS: 564
29	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-o-tolylethoxy)benzoylamino]propionic acid methyl ester; MS: 524
30	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[3-(4-propoxyphenoxy)propoxy]benzoylamino}propionic acid methyl ester; MS: 598
31	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-methoxybenzyloxy)benzoylamino]propionic acid methyl ester; MS: 526
32	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-ethoxybenzyloxy)benzoylamino]propionic acid methyl ester; MS: 540
33	3-(4-Benzyloxyphenyl)-2-{4-[(diphenylcarbamoyl)methoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.64 (d, 2H), 7.41-7.26 (m. 15H), 7.03 (d, 2H), 6.91-6.81 (m, 4H), 6.55 (d, 1H), 5.08-4.95 (m, 3H), 4.61 (s, 2H), 3.74 (s, 3H), 3.26-3.06 (m, 2H)

34	3-(4-Benzyloxyphenyl)-2-{4-[(benzylphenylcarbamoyl)methoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.65 (d, 2H), 7.40-6.77 (m, 21H), 6.54 (d, 1H), 5.08-4.95 (m, 3H), 4.90 (s, 2H), 4.42 (s, 2H), 3.74 (s, 3H), 3.25-3.06 (m, 2H)
35	3-(4-Benzyloxyphenyl)-2-{4-[(dibenzylcarbamoyl)methoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.69 (d, 2H), 7.42-7.16 (m, 15H), 7.05 (d, 2H), 6.90 (d, 4H), 6.53 (d, 1H), 5.09-4.97 (m, 3H), 4.83 (s, 2H), 4.62 (s, 2H), 4.51 (s, 2H), 3.76 (s, 3H), 3.29-3.10 (m, 2H)
36	3-(4-Benzyloxyphenyl)-2-{4-[2-(10,11-dihydrodibenzo[b,f]azepin-5-yl)-2-oxoethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.65 (d, 2H), 7.41-6.81 (m, 19H), 6.49 (d, 1H), 5.09-4.97 (m, 3H), 4.80 (d, 1H), 4.45 (d, 1H), 3.75 (s, 3H), 3.45-3.17 (m, 4H), 2.93-2.81 (m, 2H)
37	3-(4-Benzyloxyphenyl)-2-{4-[(diphenylcarbamoyl)methoxy]-benzoylamino}propionic acid; ^{1}H-NMR: 7.61 (d, 2H), 7.37-6.66 (m, 22H), 5.00-4.85 (m, 3H), 4.59 (s, 2H), 3.30-3.10 (m, 2H)
38	3-(4-Benzyloxyphenyl)-2-(4-{[(3-methoxyphenyl)phenylcarbamoyl]methoxy}-benzoylamino)propionic acid methyl ester; MS: 645
39	3-(4-Benzyloxyphenyl)-2-{4-[(cyclohexylphenylcarbamoyl)methoxy]-benzoylamino}propionic acid methyl ester; MS: 621

The compounds of formula (Ia) shown in Table 12 were synthesized according to any of methods A to C, starting from intermediate (VIb):

TABLE 12

Ex.	
40	{[4-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}acetic acid ethyl ester; ^{1}H-NMR: 7.42-6.75 (m, 23H), 4.80-4.65 (m, 2H), 4.30-3.99 (m, 6H), 3.72 (s, 4H), 2.90 (t, 2H), 1.27 (m, 3H)
41	{(3-Benzyloxybenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}acetic acid ethyl ester; ^{1}H-NMR: 7.42-6.89 (m, 23H), 5.07-5.03 (m, 2H), 4.74-4.53 (m, 2H), 4.30-3.82 (m, 6H), 3.70 (s, 4H), 2.87 (t, 2H), 1.32-1.19 (m, 3H)
42	{[3-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}acetic acid ethyl ester; ^{1}H-NMR: 7.40-6.84 (m, 23H), 4.78-4.56 (m, 2H), 4.30-3.85 (m, 6H), 3.70 (s, 4H), 2.86 (t, 2H), 1.33-1.19 (m, 3H)
43	{[3-(2-Dibenzylaminoethoxy)benzoyl]-(4-phenoxybenzyl)amino}acetic acid ethyl ester; ^{1}H-NMR: 7.41-6.90 (m, 23H), 4.77-4.57 (m, 2H), 4.30-3.85 (m, 6H), 3.71 (s, 4H), 2.88 (t, 2H), 1.33-1.19 (m, 3H)
44	{(4-*tert*-Butylbenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}acetic acid ethyl ester; ^{1}H-NMR: 7.41-6.80 (m, 18H), 4.78-4.57 (m, 2H), 4.25-3.42 (m, 10H), 2.87 (m, 2H), 1.32-1.19 (m, 12H)
45	{[3-(2-Dibenzylaminoethoxy)benzoyl]-(3-benzyloxybenzyl)amino}acetic acid ethyl ester; ^{1}H-NMR: 7.41-6.80 (m, 23H), 5.07-5.03 (m, 2H), 4.78-4.57 (m, 2H), 4.30-3.68 (m, 10H), 2.86 (m, 2H), 1.33-1.19 (m, 3H)

46	{(4-Benzyloxybenzyl)-[4-(2-dibenzylaminoethoxy)benzoyl]amino}acetic acid ethyl ester; ^{1}H-NMR: 7.47-7.23 (m, 19H), 6.97 (d, 2H), 6.79 (d, 2H), 5.08 (s, 2H), 4.71-4.62 (m, 2H), 4.22-3.99 (m, 6H), 3.72 (s, 4H), 2.89 (t, 2H), 1.27 (m, 3H)
47	3-(5-Benzyloxy-1*H*-indol-3-yl)-2-[4-(2-dibenzylaminoethoxy)-benzoylamino]propionic acid methyl ester; ^{1}H-NMR: 8.01 (s, 1H), 7.64 (d, 2H), 7.41-7.22 (m, 14H), 7.00 (dd, 2H), 6.90 (dd, 1H), 6.74 (d, 2H), 6.64 (d, 1H), 5.17 (m, 1H), 4.85 (d, 1H), 4.62 (d, 1H), 3.94 (t, 2H), 3.74 (s, 3H), 3.70 (s, 4H), 3.45 (dd, 1H), 3.35 (dd, 1H), 2.86 (t, 2H)
48	2-[4-(2-Dibenzylaminoethoxy)benzoylamino]-3-(1-methyl-1*H*-indol-3-yl)propionic acid methyl ester; ^{1}H-NMR: 7.60 (d, 2H), 7.53 (d, 1H), 7.41-7.21 (m, 12H), 7.08 (t, 1H), 6.85 (s, 1H), 6.77 (d, 2H), 6.56 (d, 1H), 5.12 (m, 1H), 4.03 (t, 2H), 3.75-3.72 (m, 10H), 3.43 (d, 2H), 2.90 (t, 2H)
49	3-(5-Benzyloxy-1*H*-indol-3-yl)-2-[3-(2-dibenzylaminoethoxy)benzoylamino]-propionic acid methyl ester; ^{1}H-NMR: 7.95 (s, 1H), 7.41-7.19 (m, 14H), 7.04-6.88 (m, 4H), 6.69 (d, 1H), 5.16 (m, 1H), 4.89 (d, 1H), 4.71 (d, 1H), 3.98 (t, 2H), 3.74 (s, 3H), 3.69 (s, 4H), 3.45 (dd, 1H), 3.35 (dd, 1H), 2.86 (t, 2H)
50	{(3-Benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}acetic acid ethyl ester; ^{1}H-NMR: 7.45-7.28 (m, 14H), 7.06-6.81 (m, 8H), 5.08 (s, 4H), 5.06 (s, 2H), 4.77-4.66 (m, 2H), 4.21 (m, 2H), 4.11-3.88 (m, 2H), 1.26 (m, 3H)

51	3-{(3-Benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid ethyl ester; ^{1}H-NMR: 7.45-7.26 (m, 14H), 6.96-6.82 (m, 8H), 5.08 (s, 4H), 5.05 (s, 2H), 4.63 (br s, 2H), 4.12 (m, 2H), 3.66 (m, 2H), 2.67 (m, 2H), 1.26 (m, 3H)
52	3-{(4-Benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid ethyl ester; ^{1}H-NMR: 7.46-7.27 (m, 13H), 7.13-6.93 (m, 9H), 5.08 (s, 2H), 5.07 (s, 2H), 5.06 (s, 2H), 4.60 (br s, 2H), 4.13 (m, 2H), 3.65 (m, 2H), 2.67 (m, 2H), 1.27 (m, 3H)
53	{(4-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}acetic acid ethyl ester; ^{1}H-NMR: 7.42-7.28 (m, 13H), 7.11-6.95 (m, 9H), 5.07-4.99 (m, 6H), 4.75-4.53 (m, 2H), 4.23 (q, 2H), 4.13-3.84 (m, 2H), 1.26 (m, 3H)
54	{(3-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}acetic acid ethyl ester; ^{1}H-NMR: 7.46-7.26 (m, 13H), 7.11-6.80 (m, 9H), 5.09-4.94 (m, 6H), 4.79-4.57 (m, 2H), 4.23 (q, 2H), 4.14-3.84 (m, 2H), 1.26 (m, 3H)
55	3-{(3-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid ethyl ester; ^{1}H-NMR: 7.45-7.25 (m, 13H), 7.02-6.90 (m, 7H), 6.78 (m, 2H), 5.07-4.94 (m, 6H), 4.75-4.52 (m, 2H), 4.15 (m, 2H), 3.71-3.50 (m, 2H), 2.72-2.39 (m, 2H), 1.26 (m, 3H)
56	3-[(4-Benzyloxybenzoyl)-(3-benzyloxybenzyl)amino]propionic acid ethyl ester; MS: 524
57	3-{(4-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid ethyl ester; MS: 631

58	(2*S*)-2-[3-(4-Butylbenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; ^{1}H-NMR: 7.45 (s, 1H), 7.35 (d, 4H), 7.20 (d, 2H), 7.12 (m, 1H), 6.47 (d, 1H), 5.06 (s, 2H), 4.87 (m, 1H), 3.76 (s, 1H), 2.62 (t, 2H), 1.78-0.90 (m, 20H)
59	2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-bromophenyl)propionic acid methyl ester; ^{1}H-NMR: 7.69 (d, 2H), 7.45-7.20 (m, 8H), 7.06-6.93 (m, 7H), 6.50 (d, 1H), 5.09-5.03 (m, 5H), 3.77 (s, 3H), 3.25 (dd, 1H), 3.16 (dd, 1H)
60	2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-fluorophenyl)propionic acid methyl ester; ^{1}H-NMR: 7.69 (d, 2H), 7.45-7.20 (m, 6H), 7.11-6.93 (m, 9H), 6.49 (d, 1H), 5.09-5.02 (m, 5H), 3.76 (s, 3H), 3.27 (dd, 1H), 3.18 (dd, 1H)
61	3-(4-Benzyloxyphenyl)-2-[4-(2-naphthalen-2-yl-ethoxy)benzoylamino]propionic acid methyl ester; MS: 560
62	3-{[4-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}propionic acid methyl ester; ^{1}H-NMR: 7.40-7.23 (m, 16H), 7.13 (t, 1H), 7.01 (d, 2H), 6.90 (dd, 2H), 6.75 (d, 2H), 4.60 (br s, 2H), 4.01 (t, 2H), 3.71-3.62 (m, 9H), 2.88 (t, 2H), 2.67 (m, 2H)
63	3-{[3-(2-Dibenzylaminoethoxy)benzoyl]naphthalen-2-ylmethylamino}propionic acid methyl ester; ^{1}H-NMR: 7.80 (m, 3H), 7.50-7.47 (m, 2H), 7.32-7.22 (m, 13H), 7.00 (d, 1H), 6.93 (s, 1H), 6.84 (d, 1H), 4.93-4.70(m, 2H), 4.03-3.91 (t, 2H), 3.80-3.55 (m, 9H), 2.81-2.50 (m, 4H)

64	3-{(4-*tert*-Butylbenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid methyl ester; ^{1}H-NMR: 7.39-7.20 (m, 14H), 7.10 (m, 1H), 6.95 (d, 1H), 6.91 (s, 1H), 6.85 (d, 1H), 4.72-4.50 (m, 2H), 3.97 (m, 2H), 3.70-3.55 (m, 9H), 2.86 (m, 2H), 2.71-2.48 (m, 2H), 1.30 (s, 9H)
65	3-{(4-Bromobenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid methyl ester; ^{1}H-NMR: 7.47 (d, 2H), 7.39-7.20 (m, 12H), 7.05 (m, 1H), 6.93 (d, 1H), 6.86-6.80 (m, 2H), 4.68-4.50 (m, 2H), 3.97 (m, 2H), 3.70-3.55 (m, 9H), 2.87 (m, 2H), 2.72-2.46 (m, 2H)
66	3-{[3-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}propionic acid methyl ester; ^{1}H-NMR: 7.45-7.22 (m, 16H), 7.11 (t, 1H), 7.00 (m, 2H), 6.90-6.84 (m, 4H), 4.72-4.49 (m, 2H), 3.96 (m, 2H), 3.70-3.60 (m, 9H), 2.87 (m, 2H), 2.72-2.45 (m, 2H)
67	3-{[4-(2-Dibenzylaminoethoxy)benzoyl]-(4-phenoxybenzyl)amino}propionic acid methyl ester; ^{1}H-NMR: 7.40-7.14 (m, 17H), 7.02-6.97 (m, 4H), 6.78 (d, 2H), 4.61 (br s, 2H), 4.01 (t, 2H), 3.71-3.65 (m, 9H), 2.89 (t, 2H), 2.66 (m, 2H)
68	(2*S*)-2-[4-(4-Butylbenzyloxy)benzoylamino]-3-phenylpropionic acid methyl ester; MS: 446
69	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(4-butylbenzyloxy)benzoylamino]propionic acid methyl ester; MS: 552
70	(2*S*)-2-[4-(4-Butylbenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; MS: 452

71	{(3-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}acetic acid methyl ester; ^{1}H-NMR: 7.45-7.18 (m, 12H), 6.93-6.80 (m, 5H), 5.07 (s, 2H), 5.03 (s, 2H), 4.74-4.65 (m, 2H), 4.11-3.90 (m, 2H), 3.75 (s, 3H), 2.62 (t, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, 3H)
72	{(4-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}acetic acid methyl ester; ^{1}H-NMR: 7.50-7.12 (m, 13H), 6.95 (d, 4H), 5.07 (s, 2H), 5.03 (s, 2H), 4.70-4.62 (m, 2H), 4.11-3.92 (m, 2H), 3.74 (s, 3H), 2.61 (t, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, 3H)
73	3-{(3-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}propionic acid methyl ester; MS: 566
74	3-{(4-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}propionic acid methyl ester; ^{1}H-NMR: 7.45-7.13 (m, 13H), 6.95 (d, 4H), 5.06 (s, 2H), 5.03 (s, 2H), 4.58 (br s, 2H), 3.66-3.60 (m, 5H), 2.62 (m, 4H), 1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, 3H)
75	(2*S*)-2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; ^{1}H-NMR: 7.72 (d, 2H), 7.44-7.28 (m, 6H), 7.06-6.92 (m, 5H), 6.40 (d, 1H), 5.09 (s, 2H), 5.07 (s, 2H), 4.87 (s, 1H), 3.76 (s, 1H), 1.77-0.95 (m, 13H)
76	(2*S*)-2-[3-(3-Benzyloxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; ^{1}H-NMR: 7.44-7.28 (m, 9H), 7.10-6.93 (m, 4H), 6.50 (d, 1H), 5.08 (s, 4H), 4.87 (s, 1H), 3.76 (s, 1H), 1.81-0.91 (m, 13H)

77	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(4-butylbenzyloxy)benzoylamino]propionic acid methyl ester; MS: 552
78	(2*S*)-2-[3-(4-Benzyloxybenzyloxy)benzoylamino]-3-phenylpropionic acid methyl ester; MS: 496
79	(2*S*)-2-[3-(4-Benzyloxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid methyl ester; MS: 502
80	{(3-Benzyloxybenzyl)-[3-(4-butylbenzyloxy)benzoyl]amino}acetic acid methyl ester; ^{1}H-NMR: 7.41-7.16 (m, 12H), 7.10-6.80 (m, 5H), 5.06-4.92 (m, 4H), 4.78-4.57 (m, 2H), 4.14-3.90 (m, 2H), 3.77-3.68 (m, 3H), 2.61 (t, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.93 (t, 3H)
81	3-{(3-Benzyloxybenzyl)-[3-(4-butylbenzyloxy)benzoyl]amino}propionic acid methyl ester; ^{1}H-NMR: 7.41-7.17 (m, 10H), 7.01-6.77 (m, 7H), 5.05-5.04 (m, 4H), 4.91-4.71 (m, 2H), 4.66-4.48 (m, 2H), 3.69-3.60 (m, 3H), 2.72 (m, 2H), 2.61 (t, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.93 (t, 3H)
82	(2*S*)-[3-(4-Benzyloxybenzyloxy)benzoylamino]phenylacetic acid methyl ester; MS: 482
83	(2*S*)-2-{4-[2-(3-Methylquinoxalin-2-yloxy)ethoxy]benzoylamino}-3-phenylpropionic acid methyl ester; MS: 486
84	(2*S*)-[3-(3-Benzyloxybenzyloxy)benzoylamino]phenylacetic acid methyl ester; MS: 482
85	(2*S*)-2-[3-(3-Benzyloxybenzyloxy)benzoylamino]-3-phenylpropionic acid methyl ester; MS: 496

86	{(3-Benzyloxybenzyl)-[3-(4-benzyloxybenzyloxy)benzoyl]amino}acetic acid methyl ester; ^{1}H-NMR: 7.45-7.25 (m, 14H), 7.10-6.75 (m, 8H), 5.08-4.89 (m, 6H), 4.78-4.57 (m, 2H), 4.14-3.85 (m, 2H), 3.77-3.68 (m, 3H)
87	3-{(3-Benzyloxybenzyl)-[3-(4-benzyloxybenzyloxy)benzoyl]amino}propionic acid methyl ester; ^{1}H-NMR: 7.45-7.24 (m, 14H), 7.00-6.77 (m, 8H), 5.08-4.88 (m, 6H), 4.71-4.51 (m, 2H), 3.69-3.50 (m, 5H), 2.72-2.39 (m, 2H)
88	(2*S*)-[4-(4-Butylbenzyloxy)benzoylamino]phenylacetic acid methyl ester; MS: 432
89	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-pyridin-2-yl-ethoxy)benzoylamino]propionic acid methyl ester; MS: 511
90	{[4-(3-Benzyloxybenzyloxy)benzoyl]-(4-benzyloxyphenyl)amino}acetic acid ethyl ester; MS: 602
91	{[4-(3-Benzyloxybenzyloxy)benzoyl]-(3-benzyloxyphenyl)amino}acetic acid ethyl ester; MS: 602
92	3-(4-Benzyloxyphenyl)-2-{3-[(benzylphenethylcarbamoyl)methoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.41-7.23 (m, 16H), 7.16-7.05 (m, 5H), 6.98-6.98 (m, 2H), 6.60-6.55 (m,14H), 5.06-4.93 (m, 3H), 4.70 (d, 1H), 4.43 (d, 1H), 3.76 (s, 3H), 3.64-3.40 (m, 2H), 3.26-3.11 (m, 2H), 2.85 (t, 2H); MS: 657
93	{3-[(Benzylphenylcarbamoyl)methoxybenzoylamino}thiophen-3-ylacetic acid methyl ester; ^{1}H-NMR: 7.40-7.31 (m, 5H), 7.29-7.15 (m, 6H), 7.15-7.09 (m, 1H), 7.09-6.95 (m, 4H), 5.88 (d, 1H),5.30 (s, 1H), 4.90 (s, 2H), 4.43 (s, 2H), 3.80 (s, 3H); MS: 515

The compounds of formula (Iaa), (Iab) and (Iae) shown in Table 13 were synthesized according to any of methods D to F, starting from intermediate (VIII) and the corresponding alcohols, thiols or amines:

TABLE 13

Ex.	
94	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-bromophenoxy)ethoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.72 (d, 2H), 7.42-6.88 (m, 15H), 6.51 (d, 1H), 5.10-5.03 (m, 3H), 4.33 (s, 4H), 3.77 (s, 3H), 3.29-3.11 (m, 2H)
95	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.99-6.87 (m, 17H), 6.54 (d, 1H), 5.10-5.02 (m, 3H), 4.88 (t, 2H), 4.47 (t, 2H), 3.77 (s, 3H), 3.29-3.11 (m, 2H), 2.64 (s, 3H)
96	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(2,6-dimethylphenoxy)ethoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.44-7.36 (m, 9H), 7.14-6.90 (m, 7H), 6.57 (d, 1H), 5.07-5.03 (m, 3H), 4.36-4.33 (m, 2H), 4.18-4.15 (m, 2H), 3.78 (s, 3H), 3.26-3.10 (m, 2H), 2.32 (s, 6H)
97	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(pyridin-2-yloxy)ethoxy]-benzoylamino}propionic acid methyl ester; MS: 527
98	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(quinolin-8-yloxy)ethoxy]-benzoylamino}propionic acid methyl ester; MS: 577

99	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(4-imidazol-1-yl-phenoxy)ethoxy]benzoylamino}propionic acid methyl ester; MS: 592
100	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(2-methylbenzothiazol-5-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; MS: 597
101	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; MS: 580
102	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(quinolin-7-yloxy)ethoxy]-benzoylamino}propionic acid methyl ester; MS: 577
103	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(quinolin-2-yloxy)ethoxy]-benzoylamino}propionic acid methyl ester; MS: 577
104	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[3-(3-methylquinoxalin-2-yloxy)propoxy]benzoylamino}propionic acid methyl ester; MS: 606
105	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(1-methyl-1*H*-imidazol-2-ylsulfanyl)ethoxy]benzoylamino}propionic acid; MS: 532
106	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(2-fluorophenylsulfanyl)ethoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.66 (d, 2H), 7.50-7.25 (m, 7H), 7.25-7.08 (m, 2H), 7.03 (d, 2H), 6.90 (d, 2H), 6.86 (d, 2H), 6.45 (d, 1H), 5.08-6.98 (m, 3H), 4.17 (t, 2H), 3.76 (s, 3H), 3.28 (t, 2H), 3.25-3.10 (m, 2H); MS: 560

107	(2*S*)-2-{4-[2-(4-Bromophenylsulfanyl)ethoxy]benzoylamino}-3-cyclohexylpropionic acid methyl ester; ^{1}H-NMR: 7.74 (d, 2H), 7.43 (d, 2H), 7.28 (d, 2H), 6.87 (d, 2H), 6.39 (d, 1H), 4.95-4.80 (m, 1H), 4.17 (t, 2H), 3.76 (s, 3H), 3.28 (t, 2H), 1.90-1.50 (m, 5H), 1.50-1.20 (m, 5H), 1.20-0.85 (m, 3H); MS: 521
108	(2*S*)-3-Cyclohexyl-2-{4-[2-(2-methoxyphenylsulfanyl)ethoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.73 (d, 2H), 7.38 (d, 1H), 7.30-7.20 (m, 1H), 7.00-6.83 (m, 4H), 6.39 (d, 1H), 4.95-4.80 (m, 1H), 4.17 (t, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 3.28 (t, 2H), 1.90-1.50 (m, 5H), 1.50-1.20 (m, 5H), 1.20-0.85 (m, 3H); MS: 472
109	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(2-methoxyphenoxy)ethoxy]-benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.70 (d, 2H), 7.48-7.30 (m, 4H), 7.20 (t, 1H), 7.04 (d, 2H), 6.97 (d, 2H), 6.90 (d, 2H), 6.60-6.50 (m, 4H), 6.48 (d, 1H), 5.10-5.00 (m, 3H), 4.40-4.28 (m, 4H), 3.79 (s, 3H), 3.76 (s, 3H), 3.26-3.12 (m, 2H); MS: 556
110	(2*S*)-2-[4-(2-*N*-benzylaminoethoxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid methyl ester; ^{1}H-NMR: 7.68 (d, 2H), 7.41-7.30 (m, 10H), 7.05 (d, 2H), 6.90 (d, 4H), 6.51 (d, 1H), 5.10-5.00 (m, 3H), 4.14 (t, 2H), 3.90 (s, 2H), 3.76 (s, 3H), 3.19 (m, 2H) 3.06 (t, 2H)

The compounds of formula (Iaa) y (Iab) shown in Table 14 were synthesized according to methods A or C, starting from intermediate (Xb) or (XIb):

TABLE 14

Ex.	
111	((4-Benzyloxybenzyl)-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino)acetic acid ethyl ester; ^{1}H-NMR: 7.94 (d, 1H), 7.80 (d, 1H), 7.63-7.52 (m, 4H), 7.46-7.31 (m, 6H), 7.14 (d, 1H), 7.00-6.96 (m, 4H), 5.07 (s, 2H), 4.86 (t, 2H), 4.73-4.62 (m, 2H), 4.44 (t, 2H), 4.30-4.18 (m, 2H), 4.11-3.89 (m, 2H), 2.64 (s, 3H), 1.26 (m, 3H)
112	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.94 (dd, 1H), 7.81 (d, 1H), 7.60-7.52 (m, 2H), 7.43-7.25 (m, 8H), 7.13 (dd, 1H), 7.04 (d, 2H), 6.90 (d, 2H), 6.57 (d, 1H), 5.08-5.03 (m, 3H), 4.87 (t, 2H), 4.48 (t, 2H), 3.77 (s, 3H), 3.28-3.14 (m, 2H), 2.64 (s, 3H)
113	3-((3-Benzyloxybenzyl)-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino)propionic acid ethyl ester; ^{1}H-NMR: 7.95 (d, 1H), 7.79 (d, 1H), 7.64-7.52 (m, 2H), 7.41-7.25 (m, 8H), 7.03-6.78 (m, 5H), 5.04 (s, 2H), 4.81 (m, 2H), 4.55-4.00 (m, 6H), 3.72 (m, 2H), 2.72-2.63 (m, 5H), 1.27 (m, 3H)
114	((3-Benzyloxybenzyl)-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino)acetic acid ethyl ester; ^{1}H-NMR: 7.94 (d, 1H), 7.80 (d, 1H), 7.61-7.29 (m, 10H), 6.97-6.82 (m, 5H), 5.08 (s, 2H), 4.86 (t, 2H), 4.78-4.66 (m, 2H), 4.44 (t, 2H), 4.30-4.18 (m, 2H), 4.12-3.89 (m, 2H), 2.64 (s, 3H), 1.28 (m, 3H)

115	3-((3-Benzyloxybenzyl)-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino)propionic acid ethyl ester; ^{1}H-NMR: 7.94 (d, 1H), 7.80 (d, 1H), 7.64-7.52 (m, 2H), 7.45-7.24 (m, 8H), 6.97-6.78 (m, 5H), 5.07 (s, 2H), 4.86 (t, 2H), 4.62 (br s, 2H), 4.43 (t, 2H), 4.20-4.05 (m, 2H), 3.67 (m, 2H), 2.75-2.64 (s, 5H), 1.25 (m, 3H)
116	((3-Benzyloxybenzyl)-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino)acetic acid ethyl ester; ^{1}H-NMR: 7.94 (d, 1H), 7.81 (d, 1H), 7.65-7.50 (m, 2H), 7.43-7.25 (m, 8H), 7.12-6.80 (m, 5H), 5.05 (m, 2H), 4.86-4.79 (m, 2H), 4.60-4.53 (m, 2H), 4.44-4.30 (m, 2H), 4.24-4.15 (m, 2H), 4.14-3.85 (m, 2H), 2.63 (s, 3H), 1.32-1.20 (m, 3H)
117	(2*S*)-3-(4-Bromophenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.94 (dd, 1H), 7.81 (d, 1H), 7.72 (d, 2H), 7.60-7.52 (m, 2H), 7.40 (d, 2H), 7.02-6.98 (m, 4H), 6.52 (d, 1H), 5.06 (m, 1H), 4.88 (t, 2H), 4.47 (t, 2H), 3.77 (s, 3H), 3.26 (dd, 1H), 3.17 (dd, 1H), 2.64 (s, 3H)
118	(2*S*)-3-(4-Fluorophenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.92 (d, 1H), 7.80 (d, 1H), 7.72 (d, 2H), 7.65-7.52 (m, 2H), 7.11-6.94 (m, 6H), 6.51 (d, 1H), 5.06 (m, 1H), 4.88 (t, 2H), 4.47 (t, 2H), 3.77 (s, 3H), 3.27 (dd, 1H), 3.18 (dd, 1H), 2.64 (s, 3H)

119	(2*S*)-3-Cyclohexyl-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.94 (d, 1H), 7.81-7.77 (m, 3H), 7.64-7.51 (m, 2H), 7.02 (d, 2H), 6.44 (d, 1H), 4.90-4.83 (m, 3H), 4.47 (t, 2H), 3.76 (s, 3H), 2.64 (s, 3H), 1.90-0.95 (m, 13H)
120	(2*S*)-3-Cyclohexyl-2-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid methyl ester; ^{1}H-NMR: 7.93 (d, 1H), 7.80 (d, 1H), 7.64-7.51 (m, 2H), 7.46 (s, 1H), 7.36 (d, 2H), 7.12 (m, 1H), 6.54 (d, 1H), 4.90-4.83 (m, 3H), 4.47 (t, 2H), 3.76 (s, 3H), 2.63 (s, 3H), 1.90-0.95 (m, 13H)
121	{Thiophen-3-ylmethyl-{3-[2-(thiophen-2-ylsulfanyl)ethoxy]benzoyl}amino} acetic acid methyl ester; ^{1}H-NMR: 7.40-7.25 (m, 4H), 7.25-7.05 (m, 2H), 7.05-6.85 (m, 2H), 7.78-4.55 (m, 2H), 4.20-4.04 (m, 4H), 3.78-3.65 (m, 2H), 3.15-3.05 (m, 2H); MS: 448
122	{Thiophen-2-yl{3-[2-(thiophen-2-ylsulfanyl)ethoxy]benzoyl}amino}acetic acid methyl ester; ^{1}H-NMR: 7.40-7.25 (m, 4H), 7.25-7.05 (m, 2H), 7.05-6.90 (m, 2H), 6.05 (d, 1H), 4.17 (t, 2H), 4.00-3.54 (m, 4H), 3.14 (t, 2H); MS: 434
123	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(3-methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoylamino}propionic acid methyl ester; MS: 592.
124	(2*S*)-3-((4-Benzyloxybenzyl)-{3-[2-(3-methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoyl}amino)propionic acid methyl ester; MS: 606

The compounds of formula (Ia) shown in Table 16 were synthesized according to methods N or P, starting from compounds of formula (Ib)

METHOD N:

To a solution of 1 eq of the compound of formula (Ib), 1.3 eq of HOBT and 1.3 eq of EDC in tetrahydrofurane, the solution being 0.2 M in the compound of formula (Ib), 2 eq of triethylamine and 5 eq of the corresponding alcohol were added. The reaction mixture was stirred at room temperature for 18h, and then water and dichloromethane were added. The organic layer was separated, and the aquous layer was extracted once with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off under reduced pressure.

METHOD P:

1 Eq of the compound of formula (Ib) was dissolved in the corresponding alcohol, and 2 drops of H_2SO_4 conc. were added. The solution was stirred over night at room temperature, and the solvent was distilled off at reduced pressure.

TABLE 15

Ex.	
125	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid ethyl ester; ^{1}H-NMR: 7.95 (d, 1H), 7.82 (d, 1H), 7.73 (d, 2H), 7.65-7.52 (m, 2H), 7.45-7.30 (m, 5H), 7.05 (d, 2H), 7.00 (d, 2H), 6.89 (d, 2H), 6.52 (d, 1H), 5.03 (m, 3H), 4.88 (t, 2H), 4.47 (t, 2H), 4.22 (q, 2H), 3.20 (m, 2H), 2.65 (s, 3H), 1.29 (t, 3H)
126	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid isopropyl ester; MS: 620
127	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid propyl ester; MS: 620

EXEMPLE (Ib):

METHOD Q:

To a solution 0.1 M of 1 eq of the corresponding acid chloride in tetrahydrofurane or dioxane, an aqueous solution of 1 eq of the aminoacidic derivative, and 2 eq of sodium hydroxide was added. The resulting mixture was stirred for 18h at room temperature. Then, HCl 1 N was added dropwise until pH acid was reached, and the solution was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

METHOD R:

To a mixture of 1 eq of acid of formula (II), 1.3 eq of HOBT and 1.3 eq of EDC, tetrahydrofurane or dioxane were added, and the resulting solution (0.2 M in the acid of formula (II)) was stirred during 2h at room temperature. Then, an aquous solution of 1 eq of the aminoacidic derivative, and 2 eq of sodium hydroxide was added. The solution was stirred over night at room temperature. Then, HCl 1 N was added dropwise until pH acid was reached, and the solution was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography.

The compounds of formula (Ib) shown in Table 16 were synthesized according to methods Q or R, starting from intermediates (VIb):

TABLE 16

Ex.	
128	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzoylamino}propionic acid; ^{1}H-NMR: 7.90-6.80 (m, 18H), 5.00 (s, 2H), 4.45 (m, 1H), 4.26 (m, 2H), 3.40 (m, 2H), 2.95 (m, 2H), 2.35 (s, 3H)
129	(2*S*)-2-(4-Benzyloxybenzoylamino)-3-(4-benzyloxyphenyl)propionic acid; ^{1}H-NMR: 7.66 (d, 2H), 7.37-7.31 (m, 10H), 7.08 (d, 2H); 6.95 (d, 2H), 6.86 (d, 2H), 5.07 (s, 2H), 4.99 (s, 2H), 4.93 (t, 1H), 3.23-3.15 (m, 2H)
130	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 8.00-6.75 (m, 24H), 4.88 (m, 3H), 4.15 (t, 2H), 3.98 (s, 4H), 3.35-3.14 (m, 2H), 3.08 (t, 2H)
131	(2*R*)-2-[4-(2-Dibenzylaminoethoxy)benzoylamino]-3-(1*H*-indol-3-yl)propionic acid; ^{1}H-NMR: 7.72-6.74 (m, 20H), 4.80 (m, 1H), 4.02 (t, 2H), 3.72 (s, 4H), 3.55-3.25 (m, 2H), 2.89 (t, 2H)
132	3-(4-*tert*-Butylphenyl)-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.62 (d, 2H), 7.50-7.11 (m, 14H), 6.83 (d,1H), 6.76 (d, 2H), 4.91 (m, 1H), 4.10 (t, 2H), 3.94 (s, 4H), 3.38-3.16 (m, 2H), 3.05 (t, 2H), 1.20 (s, 9H)
133	3-(4-Bromophenyl)-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.62 (d, 2H), 7.43-7.24 (m, 12H), 7.04 (d, 2H), 6.85 (d,1H), 6.77 (d, 2H), 4.86 (m, 1H), 4.12 (t, 2H), 3.98 (s, 4H), 3.36-3.13 (m, 2H), 3.07 (t, 2H)

134	3-Biphenyl-2-yl-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.46-7.17 (m, 21H), 6.72 (d, 2H), 6.36 (d, 1H), 4.66 (m, 1H), 4.07 (t, 2H), 3.84 (s, 4H), 3.44-3.09 (m, 2H), 2.98 (t, 2H)
136	3-Biphenyl-4-yl-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.63 (d, 2H), 7.45-7.22 (m, 19H), 6.93 (d, 1H), 6.74 (d, 2H), 4.95 (m, 1H), 4.08 (t, 2H), 3.93 (s, 4H), 3.44-3.23 (m, 2H), 3.03 (t, 2H)
137	3-(4-*tert*-Butylphenyl)-2-[3-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.45-6.82 (m, 19H), 4.90 (m, 1H), 4.19 (t, 2H), 3.96 (s, 4H), 3.36-3.02 (m, 4H), 1.16 (s, 9H)
138	3-(4-Bromophenyl)-2-[3-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.52-6.85 (m, 19H), 4.98 (m, 1H), 4.20 (t, 2H), 3.99 (s, 4H), 3.51-3.03 (m, 4H)
139	3-(3-Bromophenyl)-2-[3-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.60-6.88 (m, 19H), 4.83 (m, 1H), 4.29 (t, 2H), 4.11 (s, 4H), 3.32-3.05 (m, 4H)
140	3-Biphenyl-2-yl-2-[3-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.50-6.88 (m, 24H), 4.93 (m, 1H), 4.29 (m, 2H), 4.13 (s, 4H), 3.40-3.20 (m, 4H)
141	2-[4-(2-Dibenzylaminoethoxy)benzoylamino]-3-(3-phenoxyphenyl)propionic acid; ^{1}H-NMR: 8.06-6.74 (m, 24H), 4.90 (m, 1H), 4.10 (t, 2H), 3.89 (s, 2H), 3.76 (s, 2H), 3.40-2.92 (m, 4H)

142	3-(5-Bromo-1*H*-indol-3-yl)-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.81-7.20 (m, 17H), 6.90 (d, 2H), 4.94 (m, 1H), 4.17 (t, 2H), 3.97 (s, 4H), 3.58-3.31 (m, 2H), 3.11 (t, 2H)
143	2-[3-(2-Dibenzylaminoethoxy)benzoylamino]-3-(3-phenoxyphenyl)propionic acid; ^{1}H-NMR: 7.44-6.88 (m, 24H), 4.87 (m, 1H), 4.16 (t, 2H), 3.94 (s, 4H), 3.34-3.03 (m, 4H)
144	3-(5-Bromo-1*H*-indol-3-yl)-2-[3-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.79-7.20 (m, 19H), 4.96 (m, 1H), 4.23 (m, 6H), 3.52-3.24 (m, 4H)
145	(2*S*)-2-[3-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid; ^{1}H-NMR: 7.45-7.21 (m,14H), 7.13-7.07 (m, 4H), 7.01 (d, 1H), 6.96-6.89 (m, 3H), 6.58 (d, 1H), 5.06-4.99 (m, 7H), 3.31 (dd, 1H), 3.21 (dd, 1H)

The compounds of formula (Ib) shown in Table 17 were synthesized according to methods J or K, starting from compounds of formula (Ia):

TABLE 17

Ex.	
146	{[4-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}acetic acid; ^{1}H-NMR: 7.66-6.88 (m, 23H), 4.81-4.68 (m, 2H), 4.57 (s, 4H), 4.40 (m, 2H), 4.18-4.00 (m, 2H), 3.63 (m, 2H)
147	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-phenylallyloxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.66 (d, 2H), 7.40-6.84 (m, 17H), 6.71 (d, 1H), 6.36 (dt, 1H), 4.98 (s, 2H), 4.92 (t, 1H), 4.70 (d, 2H), 3.30-3.08 (m, 2H)
148	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(4-phenoxybenzyloxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.62 (d, 2H), 7.34-6.79 (m, 20H), 4.99 (s, 2H), 4.94 (s, 2H), 4.84 (t, 1H), 3.25-3.02 (m, 2H)
149	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(biphenyl-4-ylmethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.82-6.91 (m, 22H), 5.28 (s, 2H), 5.02 (s, 2H), 4.75 (t, 1H), 3.40-3.10 (m, 2H)
150	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-phenoxybenzyloxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.61 (d, 2H), 7.36-6.77 (m, 20H), 4.97 (s, 2H), 4.91 (s, 2H), 4.76 (t, 1H), 3.25-3.02 (m, 2H)
151	(2*S*)-2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid; ^{1}H-NMR: 7.61 (d, 2H), 7.34-6.77 (m, 20H), 5.00 (s, 2H), 4.97 (s, 2H), 4.91 (s, 2H), 4.77 (m, 1H), 3.25-3.04 (m, 2H)

152	(2*S*)-3-(4-Benzyloxyphenyl)-2-(4-phenethyloxybenzoylamino)propionic acid; ^{1}H-NMR:,63 (d, 2H), 7.39-7.24 (m, 10H), 7.19 (d, 2H), 6.92-6.86 (m, 4H), 6.47 (d, 1H), 5.01-4.92 (m, 3H), 4.19 (t, 2H), 3.26-3.07 (m, 4H)
153	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-phenylpropoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.66 (d, 2H), 7.39-7.18 (m, 10H), 7.10 (d, 2H), 6.89-6.86 (m, 4H), 5.00 (s, 2H), 4.94 (t, 1H), 4.97 (t, 2H), 3.30-3.13 (m, 2H), 2.80 (t, 2H), 2.10 (m, 2H)
154	{(4-Benzyloxybenzyl)-[4-(2-dibenzylaminoethoxy)benzoyl]amino}acetic acid; ^{1}H-NMR: 7.31-6.40 (m, 23H), 4.90-4.50 (m, 4H), 3.90-3.60 (m, 8H), 2.74 (m, 2H)
155	{(3-Benzyloxybenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}acetic acid; ^{1}H-NMR: 7.60-6.91 (m, 23H), 5.04-5.01 (m, 2H), 4.76-3.68 (m, 10H), 3.40-3.20 (m, 2H)
156	{[3-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}acetic acid; ^{1}H-NMR: 7.58-6.88 (m, 23H), 4.79-3.71 (m, 10H), 3.32-3.17 (m, 2H)
157	{[3-(2-Dibenzylaminoethoxy)benzoyl]-(4-phenoxybenzyl)amino}acetic acid; ^{1}H-NMR: 7.61-6.94 (m, 23H), 4.80-3.71 (m, 10H), 3.35-3.15 (m, 2H)
158	{(4-*tert*-Butylbenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}acetic acid; 7.65-6.92 (m, 18H), 4.78-3.38 (m, 12H), 1.35-1.20 (m, 9H)
159	{[3-(2-Dibenzylaminoethoxy)benzoyl]-(3-benzyloxybenzyl)amino}acetic acid; ^{1}H-NMR: 7.60-6.76 (m, 23H), 5.03-4.99 (m, 2H), 4.74-3.15 (m, 12H)

160	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid; ^{1}H-NMR: 7.99-6.86 (m, 17H), 6.57 (d, 1H), 4.99 (m, 3H), 4.86 (t, 2H), 4.44 (t, 2H), 3.39-3.12 (m, 2H), 2.63 (s, 3H)
161	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(3-bromophenoxy)ethoxy]benzoylamino}propionic acid; ^{1}H-NMR: 7.62 (d, 2H), 7.33-6.79 (m, 15H), 4.95 (s, 2H), 4.83 (t, 1H), 4.26 (s, 4H), 3.25-3.02 (m, 2H)
162	3-{(3-Benzyloxybenzyl)-[4-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid; MS: 629
163	3-{(3-Benzyloxybenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid; ^{1}H-NMR: 7.52-7.16 (m, 17H), 7.05-6.62 (m, 6H), 5.03 (s, 2H), 4.75-4.51 (m, 2H), 4.07-3.85 (m, 2H), 3.75-3.66 (m, 6H), 3.14-2.83 (m, 2H), 2.78-2.33 (m, 2H)
164	3-{(4-Benzyloxybenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid; ^{1}H-NMR: 7.38-7.15 (m, 17H), 7.06-6.71 (m, 6H), 4.95 (s, 2H), 4.66-4.38 (m, 2H), 4.10-3.92 (m, 2H), 3.81-3.44 (m, 6H), 2.95-2.73 (m, 2H), 2.54-2.40 (m, 2H)
165	2-[4-(2-Dibenzylaminoethoxy)benzoylamino]-3-(1-methyl-1*H*-indol-3-yl)propionic acid; ^{1}H-NMR: 7.50-7.47 (m, 3H), 7.38-7.24 (m, 9H), 7.09-6.83 (m, 5H), 6.53 (d, 2H), 4.93 (m, 1H), 3.83-3.72 (m, 6H), 3.39 (m, 5H), 2.83 (m, 2H)
166	3-(5-Benzyloxy-1*H*-indol-3-yl)-2-[4-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.40-7.19 (m, 15H), 6.97 (m, 3H), 6.80-6.72 (m, 2H), 6.40 (m, 2H), 4.92 (m, 1H), 4.69 (d, 1H), 4.46 (d, 1H), 3.68 (m, 6H), 3.26 (m, 2H), 2.76 (m, 2H)

167	3-(5-Benzyloxy-1*H*-indol-3-yl)-2-[3-(2-dibenzylaminoethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.27-7.05 (m, 15H), 6.92-6.85 (m, 4H), 6.72-6.50 (m, 4H), 4.82 (m, 1H), 4.64 (d, 1H), 4.43 (d, 1H), 3.67 (m, 2H), 3.56 (s, 4H), 3.20 (m, 2H), 2.66 (m, 2H)
168	{(4-Benzyloxybenzyl)-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino}acetic acid; ^{1}H-NMR: 7.87 (d, 1H), 7.74 (d, 1H), 7.60-7.25 (m, 10H), 7.06 (d, 1H), 6.90-6.88 (m, 4H), 5.00 (s, 2H), 4.80 (t, 2H), 4.68-4.55 (m, 2H), 4.38 (t, 2H), 4.04-3.79 (m, 2H), 2.58 (s, 3H)
169	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(2,6-dimethylphenoxy)ethoxy]benzoylamino}propionic acid; ^{1}H-NMR: 7.43-7.30 (m, 9H), 7.24-6.91 (m, 7H), 6.58 (d, 1H), 5.07-5.00 (m, 3H), 4.35-4.32 (m, 2H), 4.17-4.14 (m, 2H), 3.30 (dd, 1H), 3.21 (dd, 1H), 2.32 (s, 6H)
170	3-{(3-Benzyloxybenzyl)-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino}propionic acid; MS: 592
171	{(3-Benzyloxybenzyl)-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino}acetic acid; MS: 578
172	{(3-Benzyloxybenzyl)-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino}acetic acid; MS: 578
173	3-{(3-Benzyloxybenzyl)-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoyl}amino}propionic acid; MS: 592
174	{(3-Benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}acetic acid; ^{1}H-NMR: 7.45-7.30 (m, 14H), 7.05-6.81 (m, 8H), 5.08 (s, 2H), 5.07 (s, 2H), 5.05 (s, 2H), 4.67 (br s, 2H), 4.15 (br s, 2H)

175	3-{(3-Benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid; ^{1}H-NMR: 7.46-7.25 (m, 13H), 7.06-6.78 (m, 9H), 5.07 (s, 4H), 5.04 (s, 2H), 4.62 (br s, 2H), 3.66 (m, 2H), 2.73 (m, 2H)
176	3-{(4-Benzyloxybenzyl)-[4-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid; ^{1}H-NMR: 7.46-7.27 (m, 13H), 7.11-6.93 (m, 9H), 5.07 (s, 2H), 5.06 (s, 2H), 5.04 (s, 2H), 4.59 (br s, 2H), 3.66 (m, 2H), 2.70 (m, 2H)
177	{(4-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}acetic acid; ^{1}H-NMR: 7.44-7.26 (m, 13H), 7.11-6.91 (m, 9H), 5.08-4.98 (m, 6H), 4.75-4.52 (m, 2H), 4.16-3.86 (m, 2H)
178	{(3-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}acetic acid; ^{1}H-NMR: 7.44-7.26 (m, 13H), 7.07-6.80 (m, 9H), 5.09-4.93 (m, 6H), 4.79-4.57 (m, 2H), 4.17-3.86 (m, 2H)
179	3-{(3-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid; ^{1}H-NMR: 7.45-7.23 (m, 13H), 7.03-6.89 (m, 8H), 6.75 (m, 1H), 5.06-4.93 (m, 6H), 4.73-4.50 (m, 2H), 3.69-3.47 (m, 2H), 2.73-2.35 (m, 2H)
180	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 578
181	3-[(4-Benzyloxybenzoyl)-(3-benzyloxybenzyl)amino]propionic acid; MS: 496
182	3-{(4-Benzyloxybenzyl)-[3-(3-benzyloxybenzyloxy)benzoyl]amino}propionic acid; ^{1}H-NMR: 7.41-7.26 (m, 13H), 7.02-6.92 (m, 9H), 5.06-4.98 (m, 6H), 4.69-4.46 (m, 2H), 3.68-3.48 (m, 2H), 2.71-2.43 (m, 2H)

183	(2*S*)-2-[4-(4-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid; ^{1}H-NMR: 7.68 (d, 2H), 7.44-7.30 (m, 12H), 7.10 (d, 2H), 7.00-6.90 (m, 4H), 6.89 (d, 2H), 5.08 (s, 2H), 5.02 (s, 4H), 4.95 (t, 1H), 3.27 (dd, 1H), 3.17 (dd, 1H)
184	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(biphenyl-2-ylmethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.64-7.55 (m, 3H), 7.42-7.33 (m, 13H), 7.10 (d, 2H), 6.89-6.84 (m, 4H), 5.02 (s, 2H), 4.97 (s, 2H), 4.95 (t, 1H), 3.26 (dd, 1H), 3.17 (dd, 1H)
185	(2*S*)-2-[3-(4-Benzyloxybenzyloxy)benzoylamino]-3-(4-benzyloxyphenyl)propionic acid; ^{1}H-NMR: 7.46-7.18 (m, 15H), 7.14-7.07 (m, 3H), 6.97 (d, 2H), 6.57 (d, 2H), 5.05-4.97 (m, 5H), 3.30 (dd, 1H), 3.19 (dd, 1H)
186	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(3-phenylallyloxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.41-7.18 (m, 13H), 7.10-7.04 (m, 3H), 6.85 (d, 2H), 6.71 (d, 1H), 6.38 (dt, 1H), 4.98 (s, 2H), 4.95-4.87 (m, 1H), 4.69 (dd, 1H), 3.25 (dd, 1H), 3.15 (dd, 1H)
187	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(biphenyl-4-ylmethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.50-6.75 (m, 22H), 4.98 (s, 2H), 4.86 (s, 2H), 4.78 (m, 1H), 3.22-3.00 (m, 2H)
188	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(3-phenoxybenzyloxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.40-7.20 (m, 11H), 7.12-6.89 (m, 11H), 6.55 (d, 1H), 5.04-5.00 (m, 5H), 3.29 (dd, 1H), 3.20 (dd, 1H)

189	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(3-phenylpropoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.40-7.16 (m, 13H), 7.06 (d, 2H), 7.00 (dd, 1H), 6.86 (d, 2H), 4.98 (s, 2H), 4.92 (t, 1H), 3.96 (t, 2H), 3.25 (dd, 1H), 3.14 (dd, 1H), 2.78 (t, 2H), 2.08 (m, 2H)
190	(2*S*)-2-[3-(4-Butylbenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 438
191	(2*S*)-3-(4-Bromophenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 551
192	(2*S*)-3-(4-Fluorophenyl)-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 490
193	(2*S*)-2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-bromophenyl)propionic acid; MS: 561
194	(2*S*)-2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-(4-fluorophenyl)propionic acid; MS: 500
195	3-{[4-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}propionic acid; MS: 615
196	3-{[4-(2-Dibenzylaminoethoxy)benzoyl](4-phenoxybenzyl)amino}propionic acid; MS: 615
197	3-{[3-(2-Dibenzylaminoethoxy)benzoyl]naphthalen-2-ylmethylamino}propionic acid; MS: 573
198	3-{(4-*tert*-Butylbenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid; MS: 579
199	3-{Biphenyl-4-ylmethyl-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid; MS: 599
200	3-{(4-Bromobenzyl)-[3-(2-dibenzylaminoethoxy)benzoyl]amino}propionic acid; MS: 601
201	3-{[3-(2-Dibenzylaminoethoxy)benzoyl]-(3-phenoxybenzyl)amino}propionic acid; MS: 615

202	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(pyridin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 513
203	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(quinolin-8-yloxy)ethoxy]benzoylamino}propionic acid; MS: 563
204	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(4-imidazol-1-yl-phenoxy)ethoxy]benzoylamino}propionic acid; MS: 578
205	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-naphthalen-2-yl-ethoxy)benzoylamino]propionic acid; ^{1}H-NMR: 7.80-7.76 (m, 3H), 7.69-7.62 (m, 3H), 7.46-7.25 (m, 8H), 7.06 (d, 2H), 6.89-6.83 (m, 4H), 4.97 (s, 2H), 4.90 (t, 1H), 4.25 (t, 2H), 3.24-3.20 (m, 3H), 3.11 (dd, 1H)
206	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(2-methylbenzothiazol-5-yloxy)ethoxy]benzoylamino}propionic acid; MS: 583
207	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 566
208	(2*S*)-2-[4-(4-Butylbenzyloxy)benzoylamino]-3-phenylpropionic acid; MS: 432
209	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(4-butylbenzyloxy)benzoylamino]propionic acid; MS: 538
210	(2*S*)-2-[4-(4-Butylbenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 438
211	(2*S*)-3-Cyclohexyl-2-{4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 478
212	(2*S*)-3-Cyclohexyl-2-{3-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 478
213	(2*S*)-2-[4-(3-Benzyloxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 488

214	(2*S*)-2-[3-(3-Benzyloxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 488
215	(2*S*)-3-(4-Benzyloxyphenyl)-2-[3-(4-butylbenzyloxy)benzoylamino]propionic acid; MS: 538
216	{(3-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}acetic acid; MS: 538
217	{(4-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}acetic acid; ^{1}H-NMR: 7.50-7.10 (m, 13H), 6.97 (d, 4H), 5.06 (s, 2H), 5.03 (s, 2H), 4.63 (br s, 2H), 4.15 (br s, 2H), 2.61(t, 2H), 1.59 (q, 2H), 1.36 (m, 2H), 0.92 (t, 3H)
218	3-{(3-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}propionic acid; MS: 552
219	3-{(4-Benzyloxybenzyl)-[4-(4-butylbenzyloxy)benzoyl]amino}propionic acid; MS: 552
220	[3-(4-Benzyloxybenzyloxy)benzoylamino]phenylacetic acid; MS: 468
221	(2*S*)-2-[3-(4-Benzyloxybenzyloxy)benzoylamino]-3-phenylpropionic acid; MS: 482
222	(2*S*)-2-[3-(4-Benzyloxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 488
223	{(3-Benzyloxybenzyl)-[3-(4-butylbenzyloxy)benzoyl]amino}acetic acid; MS: 538
224	3-{(3-Benzyloxybenzyl)-[3-(4-butylbenzyloxy)benzoyl]amino}propionic acid; MS: 552
225	(2*S*)-2-{4-[2-(3-Methylquinoxalin-2-yloxy)ethoxy]benzoylamino}-3-phenylpropionic acid; MS: 472
226	[3-(3-Benzyloxybenzyloxy)benzoylamino]phenylacetic acid; MS: 468
227	(2*S*)-2-[3-(3-Benzyloxybenzyloxy)benzoylamino]-3-phenylpropionic acid; MS: 482

228	{(3-Benzyloxybenzyl)-[3-(4-benzyloxybenzyloxy)benzoyl]amino}acetic acid; MS: 588
229	3-{(3-Benzyloxybenzyl)-[3-(4-benzyloxybenzyloxy)benzoyl]amino}propionic acid; MS: 602
230	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(quinolin-2-yloxy)ethoxy]benzoylamino}propionic acid; MS: 563
231	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(quinolin-7-yloxy) ethoxy]benzoylamino}propionic acid; MS: 563
232	[4-(4-Butylbenzyloxy)benzoylamino]phenylacetic acid; MS: 418
233	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(4-butoxybenzyloxy)benzoylamino]propionic acid; MS: 554
234	{[4-(3-Benzyloxybenzyloxy)benzoyl]-(4-benzyloxyphenyl)amino}acetic acid; MS: 574
235	{[4-(3-Benzyloxybenzyloxy)benzoyl]-(3-benzyloxyphenyl)amino}acetic acid; MS: 574
236	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-pyridin-2-yl-ethoxy)benzoylamino]propionic acid; MS: 497
237	(2*S*)-2-[4-(4-Butoxybenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 454
238	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-bromobenzyloxy)benzoylamino]propionic acid; MS: 561
239	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-bromobenzyloxy)benzoylamino]propionic acid; MS: 561
240	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-chlorobenzyloxy)benzoylamino]propionic acid; MS: 516
241	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-chlorobenzyloxy)benzoylamino]propionic acid; MS: 516
242	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-fluorobenzyloxy)benzoylamino]propionic acid; MS: 500
243	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-methylbenzyloxy)benzoylamino]propionic acid; MS: 496

244	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-methylbenzyloxy)benzoylamino]propionic acid; MS: 496
245	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(3-trifluoromethylbenzyloxy)benzoylamino]propionic acid; MS: 550
246	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-trifluoromethylbenzyloxy)benzoylamino]propionic acid; MS: 550
247	(2*S*)-2-[4-(3-Bromobenzyloxy)benzoylamino]-3-cyclohexylpropionic acid; MS: 461
248	(2*S*)-3-(4-Benzyloxyphenyl)-2-[4-(2-methoxybenzyloxy)benzoylamino]propionic acid; MS: 512
249	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[(benzylphenylcarbamoyl)methoxy]-benzoylamino}propionic acid; ^{1}H-NMR: 7.60 (d, 2H), 7.38-6.99 (m, 17H), 6.87 (d, 2H), 6.75 (d, 2H), 6.63 (d, 1H), 5.10-4.90 (m, 5H), 4.41 (s, 2H), 3.32-3.10 (m, 2H)
250	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[(dibenzylcarbamoyl)methoxy]-benzoylamino}propionic acid; ^{1}H-NMR: 7.64 (d, 2H), 7.41-6.84 (m, 21H), 6.64 (d, 1H), 5.03-4.91 (m, 3H), 4.81 (s, 2H), 4.61 (s, 2H), 4.50 (s, 2H), 3.33-3.12 (m, 2H)
251	(2*S*)-3-(4-Benzyloxyphenyl)-2-{4-[2-(10,11-dihydrodibenzo[b,f]azepin-5-yl)-2-oxoethoxy]benzoylamino}propionic acid; ^{1}H-NMR: 7.60 (d, 2H), 7.38-7.06 (m, 15H), 6.87 (d, 2H), 6.79 (d, 2H), 6.60 (d, 1H), 5.04-4.93 (m, 3H), 4.77 (d, 1H), 4.46 (d, 1H), 3.37-3.20 (m, 4H), 2.89-2.74 (m, 2H)

252	(2*S*)-2-{4-[2-(Benzoylbenzylamino)ethoxy]benzoylamino}-3-(4-benzyloxyphenyl)propionic acid; ^{1}H-NMR: 7.65 (d, 2H), 7.38-6.61 (m, 22H), 4.98 (m, 3H), 4.69-3.63 (m, 6H), 3.34-3.13 (m, 2H)
253	(2*S*)-3-(4-Benzyloxyphenyl)-2-(4-{2-[benzyl(pyridine-3-carbonyl)amino]ethoxy}benzoylamino)propionic acid; ^{1}H-NMR: 8.70-6.74 (m, 23H), 5.01-4.89 (m, 3H), 4.88-3.61 (m, 6H), 3.35-3.14 (m, 2H)
254	[{4-[2-(Benzoylbenzylamino)ethoxy]benzoyl}-(4-benzyloxybenzyl)amino]acetic acid; 1H-NMR: 7.79-6.74 (m, 23H), 5.06 (s, 2H), 4.89-3.61 (m, 10H)
255	[(4-Benzyloxybenzyl)-(4-{2-[benzyl(pyridine-3-carbonyl)amino]ethoxy}benzoyl)amino]acetic acid; ^{1}H-NMR:: 8.64 (d, 1H), 7.79-6.80 (m, 21H), 5.06 (s, 2H), 4.87-3.65 (m, 10H)
256	{Thiophen-3-ylmethyl-{3-[2-(thiophen-2-ylsulfanyl)ethoxy]benzoyl}amino}acetic acid; MS: 434
257	{Thiophen-2-yl-{3-[2-(thiophen-2-ylsulfanyl)ethoxy]benzoylamino}acetic acid; MS: 420.
258	{3-[(Benzylphenylcarbamoyl)methoxy]benzoylamino}thiophen-3-yl-acetic acid; MS: 501
259	3-(4-Benzyloxyphenyl)-2-{3-[(benzylphenethylcarbamoyl)methoxy]-benzoylamino}propionic acid; ^{1}H-NMR: 7.41-7.00 (m, 21H), 6.90-6.75 (m, 2H), 4.85-4.75 (m, 3H), 4.67-4.55 (m, 2H), 4.45-4.25 (m, 2H), 3.60-3.35 (m, 2H); 3.35-3.05 (m, 2H), 2.60-2.05 (m, 2H); MS: 643

260	3-(4-Benzyloxyphenyl)-2-{4-[(phenylpyridin-2-yl-carbamoyl)methoxy]-benzoylamino}propionic acid; ^{1}H-NMR: 9.92 (d, 1H), 7.62-7.40 (m, 6H), 7.35 (d, 2H), 7.30-7.10 (m, 7H), 7.12 (d, 1H), 6.97 (d, 2H), 6.90 (2H), 6.75 (d, 2H), 5.27 (s, 2H), 4.89 (s 2H), 4.76 (t, 1H), 3.11 (dd, 1H), 3.01 (dd, 1H)
261	3-(4-Benzyloxyphenyl)-2-{4-[(cyclohexylphenylcarbamoyl)methoxy]benzoylamino}propionic acid; MS: 607
262	3-(4-Benzyloxyphenyl)-2-{4-[(*tert*-butylcyclohexylcarbamoyl)methoxy]-benzoylamino}propionic acid; MS: 587
263	3-(4-Benzyloxyphenyl)-2-(4-{[(2-fluorophenyl)thiophen-2-ylmethylcarbamoyl]methoxy}benzoylamino)propionic acid; MS: 639
264	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(3-methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoylamino}propionic acid; MS: 578
265	(2*S*)-3-((4-Benzyloxybenzyl)-{3-[2-(3-methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoyl}amino)propionic; MS: 592

EXAMPLES (Ic) and (Id)

The compounds of formula (Ic) and (Id) shown in Table 18 were synthesized either according to any of methods A to C, starting from compounds of formula (Ib) and the aminic derivatives HNR_2R_3 oR HNR_2OR_1:

TABLE 18

Ex.	
266	*N*-[*(1S)*-2-(4-Benzyloxyphenyl)-1-dimethylcarbamoylethyl]-4-phenetyloxybenzamide; ^{1}H-NMR: 7.75 (d, 2H), 7.44-6.88 (m, 16H), 5.30 (m, 1H), 5.05 (s, 2H), 4.22 (t, 2H), 3.25-2.90 (m, 4H), 2.88 (s, 3H), 2.67 (s, 3H)
267	*N*-[*(1S)*-2-(4-Benzyloxyphenyl)-1-dimethylcarbamoylethyl]-4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzamide; 7.96-7.29 (m, 9H), 7.14-7.09 (m, 4H), 7.00 (d, 2H), 6.89 (d, 2H), ^{1}H-NMR: 5.30 (m, 1H), 5.05 (s, 2H), 4.88 (t, 2H), 4.47 (t, 2H), 3.30-2.95 (m, 2H), 2.88 (s, 3H), 2.68 (s, 3H), 2.65 (s, 3H)
268	*N*-[*(1S)*-2-(4-Benzyloxyphenyl)-1-hydroxycarbamoylethyl]-4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzamide; MS: 593
269	*N*-[*(1S)*-2-(4-Benzyloxyphenyl)-1-methoxycarbamoylethyl]-4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzamide; MS: 607
270	*N*-[*(1S)*-2-(4-Benzyloxyphenyl)-1-(methoxymethylcarbamoyl)ethyl]-4-[2-(3-methylquinoxalin-2-yloxy)ethoxy]benzamide; MS: 621

Assay of binding to the PPARγ2

The cDNA encoding for the open reading frame of the hPPARγ2 is amplified by PCR (*polymerase chain reaction*) and inserted in the plasmid pGEX-4T-2. This construction (pGEX-hPPARγ) is introduced into *E. coli* where it is overexpressed and semipurified as a fusion protein with glutathione

S-transferase (GST) (Elbrecht et al., *J. Biol. Chem.* **1999**, *274*, 7913-7922).

The binding of the compounds to the GST-hPPARγ2 s is determined by modifications in the method described by Lehmann et al. (*J. Biol. Chem.* **1995**, *270*, 12953-12957). The receptors (2.5 μg) were incubated in 96-well plates in the presence or in the absence of the products with [^{3}H]BRL-49853 (100 nM) for 3 h at 4°C, in a final volume of 200 μL of buffer Tris-HCl 10 mM pH:8.0, containing KCl 50 mM and DTT 10 mM. Non-specific binding was determined in the presence of BRL-49853 100 μM. The reaction mixture was transferred to a Multiscreen Durapore (Millipore) microplate containing glutathione-Sepharose 4B in every well. The reaction mixture was left to incubate with the resin during 10 min, and then centrifuged at 735 g during 2 min. To dissociate the receptor bound to the resin, reduced glutathione 10 mM is added and incubated during 10 min. The receptor was eluted by centrifugation. Then, 800 μL of scintillation liquid were added to the elution and the contained radioactivity was quantified by liquid scintillation spectroscopy (Microbeta Wallac, Perkin Elmer).

LBD-hPPARs transactivation assay

COS-7 cells were cultivated in 24-well plates and transfected with the pFACMV plasmids that encode the chimeric proteins containing the GAL4 DNA binding domain fused to the PPARγ LBD. The reporter plasmid for the foregoing constructions was pFR-Luc, which contains five repetitions of the GAL4-response element in front of a promoter that controls the transcription of the luciferase gene. Lipofectamine was used as a transfection agent.

The plasmids of the chimeric receptors and the reporter gene were inserted in the cells by transitory transfection in COS-7 cells in culture. When the products were added to the culture for 48 h, the luciferase activity showed the effect of the PPAR activity modulation on the transcription of the reporter construction (Wright et al., *J. Biol. Chem.* **2000**, *275*, 1873).

Cloning of human PPARα, PPARδ and PPARγ2

The human PPARs cDNAs were amplified through RT-PCR. For hPPARα, RNA was obtained from HepG2 cells treated with linoleic acid; for h PPARδ, RNA was obtained from untreated HepG2 cells; for hPPARγ2, RNA was obtained from human white adipose tissue. Each amplified fragment was cloned into pBluescript (Stratagene®) and sequenced. One clone for each construction was selected and used as template for further subcloning and PCR amplifications.

GST-fused protein construction

To generate these chimeric proteins, the complete cDNA of the four human PPARs were cloned into pGEX4T2 (Amersham Biosciences). The fragment was obtained from the pBluescript-cDNAs clones digested with endonucleases. To assess the plasmid identity and to ensure the in-phase cloning of the proteins, pGEXs constructions were sequenced. GST-hPPARγ2, GST-hPPARα or GST-h PPARδ fusion proteins were generated in Escherichia coli (BL21 strain DE3). Cells were cultured in LB medium to a density of A600= 1.6 odu, and induced for overexpression by addition of isopropyl-1-thio-β-D-galactopyranoside (IPTG)-induced

cultures to a final concentration of 0.5 mM. The IPTG-induced cultures were grown at room temperature o/n, before cells were harvested by centrifugation at 5000 g for 15 min. After sonication, the GST-fusion proteins were purified from the cell pellet using glutathione-Sepharose beads, following the procedure recommended by the manufacturer (Amersham Pharmacia Biotech). Excess of gluthatione was removed o/n by dyalisis at 4°C. Receptor purity was visualized by SDS-PAGE and protein content was determined by Bradford method. Receptor aliquots were stored at -80°C until use.

GST-hPPARα and GST-hPPARδ binding

Using 96-well culture plates, PPARα or PPARδ (5 μg) were diluted to a total volume of 100 μL with buffer consisting of 50 mM HEPES (pH:7.0), 50 mM KCl, 5 mM EDTA and10 mM DTT, in the presence of [3H]-GW2433 (100 and 50 nM for PPARα and PPARδ, respectively). Nonspecific binding was estimated in parallel incubations containing 50 μM of GW-2433. Plates were incubated for 2 h at room temperature. Free radioligand was separated from receptor-bound ligand by size exclusion chromatography using Sephadex G-25 in 96-wells spin plates, using the Multiscreen Column Loader (Millipore). Eluted radioactivity was quantitated by liquid scintillation counting in a Microbeta counter (Perkin Elmer).

In Table 19, affinity and functional activity data of some of the compounds of the present invention are shown.

TABLE 19

Ex.	Affinity PPARγ (1)	Functional activity PPARγ	Affinity PPARγ (1)	Affinity PPARγ (1)
20	+++	Partial agonist	+	+
21	+++	Partial agonist	+	+
27	+++	Antagonist	+	+
95	+++	Agonist	+	+
98	+++	Antagonist	+	+
129	+++	Partial agonist	+	+
131	++	Partial agonist	+	+
136	++	Antagonist	+	++
141	++	Antagonist	+	++
142	++	Antagonist	+	++
145	++	Antagonist	+	+
146	++	Antagonist	+	+
153	++	Partial agonist	+	+
160	+	Partial agonist	+	+
161	++	Antagonist	+	+
162	+++	Antagonist	+	+
163	+++	Antagonist	+	+
164	++	Antagonist	+	+
170	++	Antagonist	+	+
176	+++	Antagonist	++	+
180	+++	Partial agonist	++	+
183	+++	Partial agonist	+	+
184	+++	Antagonist	+	-
185	+++	Partial agonist	+	+
187	+++	Agonist	+	+
188	+++	Partial agonist	+	+

192	+	Partial agonist	+	+
210	+++	Agonist	+	+
218	+++	Antagonist	+	+
237	+++	Partial agonist	+	+
238	+++	Antagonist	+	+
243	+++	Antagonist	+	+
267	++	Partial agonist	+	+

(1) +++ : Ki < 1000 nM, ++: 1000 nM< Ki <3000 nM, + : Ki >3000 nM